Final Project

Determine the design parameters for the trial

To determine the time-to-analysis event model for patients with 'standard', three drug regime, we analyzed the historical data with STATA, with no assumption of the explicit parametric survival models. Hence, we applied Kaplan-Meier survivor function to generate non-parametric estimates (Table 1, Figure 1).

To determine whether or not stage (III versus IV) is a prognostic factor, as this could be important in the design, we generated Kaplan-Meier survivor estimates for patients with stage III and stage IV, respectively. We also performed Log-rank test for equality of their survivor functions (Table 2, 3, Figure 2). From the result, we can see that stage IV patients have significantly higher risk of analytic event than stage III patients and thus stage (III versus IV) is a significant prognostic factor (P=0.04).

Set up the method of treatment assignment and trial size

In the current study, there are two treatment groups, the traditional treatment (Cisplatin, 5-FU and vincristine) and the new one (traditional treatment and Adriamycin). The null hypothesis is that the new treatment does not change the adverse event rate and the alternative hypothesis is that the new treatment decreases the event rate, given the information that historically we have seen improvement in the treatment of the disease using new treatment regime. Thus, one-sided test is chosen, as discussed in the class. Moreover, it has been shown that Adriamycin has undesired severe side effects, such as heart damage, so it would be preferred to suggest the routine clinical usage of the new treatment if Adriamycin has a very significant effect on reducing adverse event rate, thus 0.025 is chosen as cutoff for evidence of effect.[1] Hence, we propose one-sided test with alpha level of 0.025 to qualify as evidence of an effect.

As stage is a significant prognostic factor, in order to ensure that the trial is well balanced across important prognostic factors and reduce the variance associated with the estimate of treatment effect, we propose stratified randomization by the stage of the disease. To ensure balanced number of patients in different stratum, we propose block randomization metric with the fraction of patients to be assigned to the new treatment regime to be 50%. The block size is 4 for convenience and that the stratification factor is the stage.

ART is used to clinical trial design, with the alternative hypothesis that the new treatment regime can reduce the hazard rate by 33%, based on historical data. Power of 0.80 is chosen to the analysis as it is recommended by the guideline [2].

We first tried various combinations of 8 years of total recruitment and follow-up time. From the analysis, 4 years of recruitment and 4 years of follow-up time with total expected sample size of 462 was chosen from all combinations because it has the least years of recruitment and yet number of patients investigators guarantees to recruit during recruitment period (N=600) is greater than the expected sample size (N=462) (Figure 3). Next we tried various follow-up time

for 4 years of recruitment time and chose 4 years recruitment and 2 years of follow-up period as final study design regime as it achieves reasonable power (Power=0.883) and 2 years of follow-up period is reasonably cost-effective (Figure 4).

To assess the early difference between the two regimes, 1-interim-look analysis will be performed at the end of the second year to save money and time. Under the null hypothesis, we expected the have 250 events in total with total enrollment of 600 patients. After two years of the recruitment, half of the patients have been enrolled into the trial. If we monitor at the end of the second year, we are expect to see 91 events (36%) out of 300 patients enrolled; while we are expect to see 151 events (60%) out of 450 patients enrolled if we monitor at the end of the third year. Therefore, it is reasonable to conduct interim analysis at the end of the second year (Figure 5).

In short, we propose to perform a trial with 4 years of recruitment and 2 years of follow-up with 600 patients enrolled in total, in a stratified blocked randomization manner with 50% of the patients to be assigned each treatment group stratified by their disease stage (III versus IV) (Figure 6). The predicted power is 0.883 at one-sided alpha level of 0.025. Interim analysis will be performed at the end of the end of the second year.

Conduct the analysis

Based on the interim data sent back from Dr. Mark Krailo, GroupSeq is used to calculate decision boundary with 0.356 (89/250) of expected events occurred and stratified cox proportional regression is used to determine the effect of new treatment based on stratified stage status. For GroupSeq analysis, we assume that the 2 sequential tests follow $f(t,\alpha) = \alpha t^2$ spending function and that one-sided alpha level is set to be 0.025 to be consistent with the study design.

From the result, the observed test statistic from the cox proportional regression is -1.10 (Figure 7). On the other hand, GroupSeq result indicates that the regression statistic -1.10 falls within the boundary of (-2.79,8), with the alternative hypothesis that the new treatment can reduce hazard rate (Figure 7,8, Table 4). This means that the new treatment regime is not significantly better than the standard regime at the interim analysis at 0.025 alpha level. Therefore, our trial needs to continue to the full accrual

Analyze the trial and determine whether the new therapy should be adopted

Based on the full data with 4 years of recruitment sent back from Dr. Mark Krailo, Stratified cox proportional regression is used to determine the effect of new treatment, using 590 patients who are eligible for the analysis. From the result, GroupSeq result indicates that the regression statistic -2.27 falls outside the boundary of (-1.99,8), with the alternative hypothesis that the new treatment can reduce hazard rate (Figure 8,9, Table 4). This means that the new treatment regime is significantly better than the standard regime at 0.025 alpha level and thus it should be adopted. Based on compliance analysis, 96.95% of the patients complied with their treatment and 3.05% of the patients did not comply with their treatment at the final data. For patients

who did not comply with their treatment assignment, we regard their treatment status as randomized and tend to underestimate the true treatment effect (Table 5).

In short, the new regime can reduce the hazard rate to 0.75 (95% CI: 0.59-0.96) compared to the traditional regime. Such reduction is significant at one-sided alpha level of 0.025 and hence suggests the inclusion of Adriamycin to the traditional treatment regime.

Effect of Adriamycin on the SMN rate

Based on the full data with 4 years of recruitment sent back from Dr. Mark Krailo, Stratified cox proportional regression is used to determine the effect of new treatment on SMN rate. From the result, GroupSeq result indicates that the regression statistic -0.05 falls within the boundary of (-1.99,8), with the alternative hypothesis that the new treatment can reduce hazard rate (Figure 8,10, Table 4). This means that the new treatment regime is not significantly better than the standard regime at 0.025 alpha level on its effect on SMN rate.

In short, the new regime can reduce the hazard rate to 0.95(95% CI: 0.13-6.75) compared to the traditional regime. Such reduction is not significant at one-sided alpha level of 0.025.

Bonus

Schoenfeld residuals method is used to assess the modeling assumptions of proportional hazard model. From the result, we can see that there is no evidence to contradict the modeling assumption (P=0.48)(Table 6).

Reference

1. *Han, Y. et al. Quercetin alleviates myocyte toxic and sensitizes anti-leukemic effect of adriamycin. Hematology **20**, 276-83 (2015).*
2. *ICH-Topic-E9. Note for Guidance On Statistical Principles For Clinical Trial. (1998).*

Figures and Tables

Table 1. Kaplan-Meier survivor function estimates

```
        failure _d:  c == 1 2 3
  analysis time _t:  (y-origin)/365.25
            origin:  time date_reg
                id:  ptnt_id
```

Time	Beg. Total	Fail	Survivor Function	Std. Error	[95% Conf.	Int.]
0	0	0	1.0000	.	.	.
.5	104	52	0.6646	0.0379	0.5844	0.7329
1	87	17	0.5549	0.0399	0.4732	0.6290
1.5	86	1	0.5485	0.0400	0.4668	0.6228
2	85	1	0.5420	0.0400	0.4604	0.6166
2.5	83	1	0.5356	0.0401	0.4540	0.6103
3	81	0	0.5356	0.0401	0.4540	0.6103
3.5	64	1	0.5274	0.0403	0.4456	0.6027
4	49	1	0.5177	0.0407	0.4352	0.5939
4.5	39	1	0.5062	0.0414	0.4225	0.5838
5	28	0	0.5062	0.0414	0.4225	0.5838
5.5	18	0	0.5062	0.0414	0.4225	0.5838
6	10	0	0.5062	0.0414	0.4225	0.5838
6.5	8	0	0.5062	0.0414	0.4225	0.5838
7	3	0	0.5062	0.0414	0.4225	0.5838
7.5	2	0	0.5062	0.0414	0.4225	0.5838
8	1	0	.	.	.	.

Table 2. Kaplan-Meier survivor function estimates for stage III and stage IV patients

```
        failure _d:  c == 1 2 3
  analysis time _t:  (y-origin)/365.25
            origin:  time date_reg
                id:  ptnt_id
```

Time	Beg. Total	Fail	Survivor Function	Std. Error	[95% Conf.	Int.]
III						
0	0	0	1.0000	.	.	.
1	68	42	0.6148	0.0466	0.5168	0.6988
2	66	2	0.5965	0.0470	0.4983	0.6817
3	62	1	0.5873	0.0472	0.4890	0.6730
4	38	1	0.5756	0.0477	0.4766	0.6625
5	23	0	0.5756	0.0477	0.4766	0.6625
6	9	0	0.5756	0.0477	0.4766	0.6625
7	3	0	0.5756	0.0477	0.4766	0.6625
8	1	0	.	.	.	.
IV						
0	0	0	1.0000	.	.	.
1	20	27	0.4130	0.0726	0.2711	0.5494
2	20	0	0.4130	0.0726	0.2711	0.5494
3	20	0	0.4130	0.0726	0.2711	0.5494
4	12	1	0.3813	0.0736	0.2398	0.5214
5	6	1	0.3466	0.0747	0.2063	0.4910
6	2	0	0.3466	0.0747	0.2063	0.4910
7	1	0	.	.	.	.
8	1	0	.	.	.	.

Table 3. Log-rank test for equality of survivor functions for stage III and stage IV patients

Log-rank test for equality of survivor functions

constg	Events observed	Events expected
III	46	54.03
IV	29	20.97
Total	75	75.00

```
          chi2(1) =     4.27
          Pr>chi2 =   0.0387
```

Table 4. GroupSeq result (note that the upper bound and lower bound are calculated based on the alternative hypothesis that the new treatment can increase the hazard rate)

K = 2
alpha = 0.025
Function: Power Family: alpha*t^2

k	Times	Lower Bounds	Upper Bounds	alpha[i]-alpha[i-1]	cumulative alpha
1	0.356	-8	2.7298	0.0031684	0.0031684
2	1	-8	1.9929	0.0218316	0.025

Table 5. Compliance of patients for final data

comply	Freq.	Percent	Cum.
0	18	3.05	3.05
1	572	96.95	100.00
Total	590	100.00	

Table 6. Test of proportional-hazard assumption for final data model

Time: **Time**

	chi2	df	Prob>chi2
global test	0.46	1	0.4979

Figure 1. Kaplan-Meier survival plot

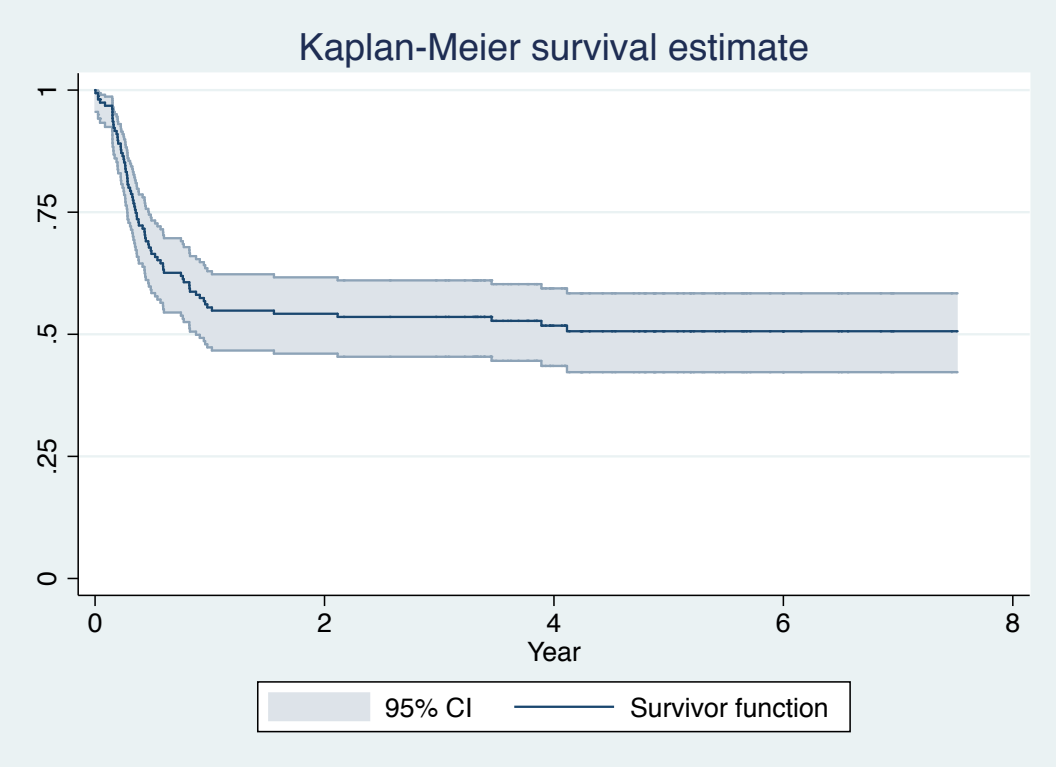

Figure 2. Kaplan-Meier survival plot for stage III and stage IV patients

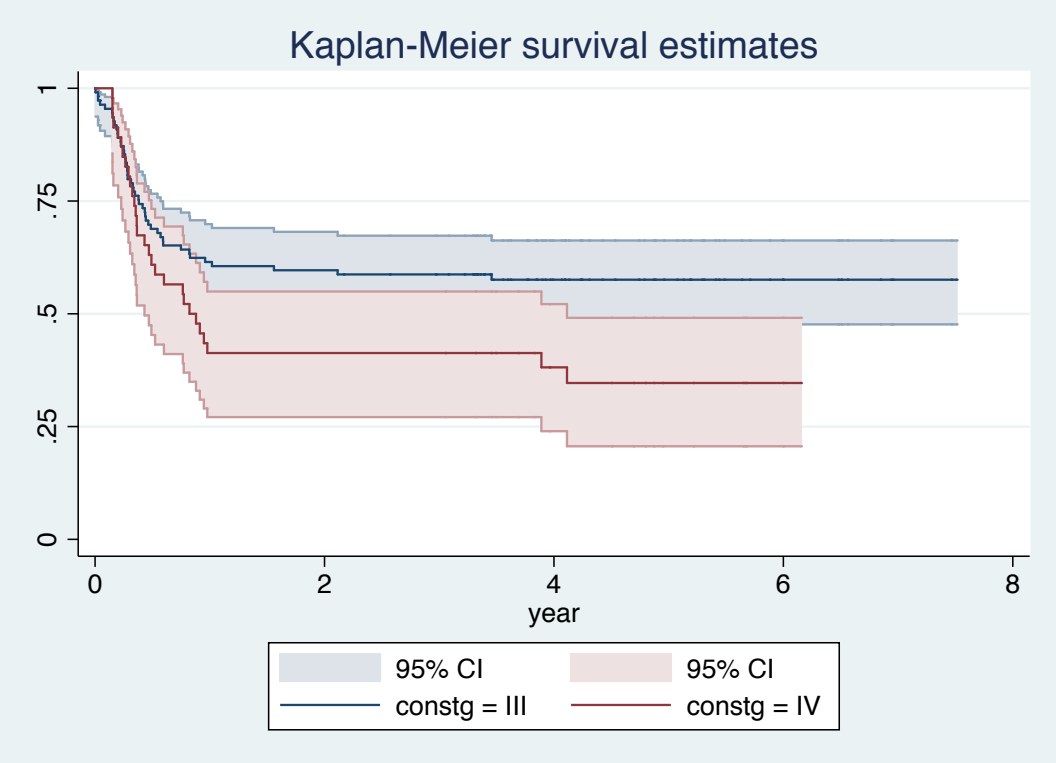

Figure 3. ART analysis for patient with 8 years of recruitment and follow-up

a

ART ANALYSIS OF **R**ESOURCES FOR **T**RIALS (version 1.1.0, 10 December 2013)

A sample size program by Abdel G Babiker, Patrick Royston & Friederike Barthel, MRC Clinical Trials Unit at UCL, London WC2B 6NH, UK.

Type of trial	**Superiority – time-to-event outcome**
Statistical test assumed	**Unweighted logrank test (local)**
Number of groups	**2**
Allocation ratio	**Equal group sizes**
Total number of periods	**8**
Length of each period	**One year**
Survival probs per period (group 1)	**0.555 0.542 0.536 0.518 0.506 0.506 0.506 0.506**
Survival probs per period (group 2)	**0.674 0.663 0.658 0.643 0.634 0.634 0.634 0.634**
Number of recruitment periods	**3**
Number of follow-up periods	**5**
Method of accrual	**Uniform**
Recruitment period-weights	**1 1 1 0 0 0 0 0**
Hazard ratios as entered (groups 1,2)	**1, 0.67**
Alpha	**0.025 (one-sided)**
Power (designed)	**0.800**
Total sample size (calculated)	**460**
Expected total number of events	**198**

b

ART ANALYSIS OF **R**ESOURCES FOR **T**RIALS (version 1.1.0, 10 December 2013)

A sample size program by Abdel G Babiker, Patrick Royston & Friederike Barthel, MRC Clinical Trials Unit at UCL, London WC2B 6NH, UK.

Type of trial	**Superiority – time-to-event outcome**
Statistical test assumed	**Unweighted logrank test (local)**
Number of groups	**2**
Allocation ratio	**Equal group sizes**
Total number of periods	**8**
Length of each period	**One year**
Survival probs per period (group 1)	**0.555 0.542 0.536 0.518 0.506 0.506 0.506 0.506**
Survival probs per period (group 2)	**0.674 0.663 0.658 0.643 0.634 0.634 0.634 0.634**
Number of recruitment periods	**5**
Number of follow-up periods	**3**
Method of accrual	**Uniform**
Recruitment period-weights	**1 1 1 1 1 0 0 0**
Hazard ratios as entered (groups 1,2)	**1, 0.67**
Alpha	**0.025 (one-sided)**
Power (designed)	**0.800**
Total sample size (calculated)	**466**
Expected total number of events	**198**

c

ART ANALYSIS OF **R**ESOURCES FOR **T**RIALS (version 1.1.0, 10 December 2013)

A sample size program by Abdel G Babiker, Patrick Royston & Friederike Barthel, MRC Clinical Trials Unit at UCL, London WC2B 6NH, UK.

Type of trial	**Superiority – time-to-event outcome**
Statistical test assumed	**Unweighted logrank test (local)**
Number of groups	**2**
Allocation ratio	**Equal group sizes**
Total number of periods	**8**
Length of each period	**One year**
Survival probs per period (group 1)	**0.555 0.542 0.536 0.518 0.506 0.506 0.506 0.506**
Survival probs per period (group 2)	**0.674 0.663 0.658 0.643 0.634 0.634 0.634 0.634**
Number of recruitment periods	**4**
Number of follow-up periods	**4**
Method of accrual	**Uniform**
Recruitment period-weights	**1 1 1 1 0 0 0 0**
Hazard ratios as entered (groups 1,2)	**1, 0.67**
Alpha	**0.025 (one-sided)**
Power (designed)	**0.800**
Total sample size (calculated)	**462**
Expected total number of events	**198**

d

ART ANALYSIS OF **R**ESOURCES FOR **T**RIALS (version 1.1.0, 10 December 2013)

A sample size program by Abdel G Babiker, Patrick Royston & Friederike Barthel, MRC Clinical Trials Unit at UCL, London WC2B 6NH, UK.

Type of trial	**Superiority – time-to-event outcome**
Statistical test assumed	**Unweighted logrank test (local)**
Number of groups	**2**
Allocation ratio	**Equal group sizes**
Total number of periods	**8**
Length of each period	**One year**
Survival probs per period (group 1)	**0.555 0.542 0.536 0.518 0.506 0.506 0.506 0.506**
Survival probs per period (group 2)	**0.674 0.663 0.658 0.643 0.634 0.634 0.634 0.634**
Number of recruitment periods	**6**
Number of follow-up periods	**2**
Method of accrual	**Uniform**
Recruitment period-weights	**1 1 1 1 1 1 0 0**
Hazard ratios as entered (groups 1,2)	**1, 0.67**
Alpha	**0.025 (one-sided)**
Power (designed)	**0.800**
Total sample size (calculated)	**470**
Expected total number of events	**198**

Figure 4. ART analysis for patient with 4 years of recruitment and various years of follow-up

a

ART – **A**NALYSIS OF **R**ESOURCES FOR **T**RIALS (version 1.1.0, 10 December 2013)

A sample size program by Abdel G Babiker, Patrick Royston & Friederike Barthel, MRC Clinical Trials Unit at UCL, London WC2B 6NH, UK.

Type of trial	**Superiority – time-to-event outcome**
Statistical test assumed	**Unweighted logrank test (local)**
Number of groups	**2**
Allocation ratio	**Equal group sizes**
Total number of periods	**7**
Length of each period	**One year**
Survival probs per period (group 1)	**0.555 0.542 0.536 0.518 0.506 0.506 0.506**
Survival probs per period (group 2)	**0.674 0.663 0.658 0.643 0.634 0.634 0.634**
Number of recruitment periods	**4**
Number of follow-up periods	**3**
Method of accrual	**Uniform**
Recruitment period-weights	**1 1 1 1 0 0 0**
Hazard ratios as entered (groups 1,2)	**1, 0.67**
Alpha	**0.025 (one-sided)**
Power (calculated)	**0.888**
Total sample size (designed)	**600**
Expected total number of events	**255**

b

ART – **A**NALYSIS OF **R**ESOURCES FOR **T**RIALS (version 1.1.0, 10 December 2013)

A sample size program by Abdel G Babiker, Patrick Royston & Friederike Barthel, MRC Clinical Trials Unit at UCL, London WC2B 6NH, UK.

Type of trial	**Superiority – time-to-event outcome**
Statistical test assumed	**Unweighted logrank test (local)**
Number of groups	**2**
Allocation ratio	**Equal group sizes**
Total number of periods	**6**
Length of each period	**One year**
Survival probs per period (group 1)	**0.555 0.542 0.536 0.518 0.506 0.506**
Survival probs per period (group 2)	**0.674 0.663 0.658 0.643 0.634 0.634**
Number of recruitment periods	**4**
Number of follow-up periods	**2**
Method of accrual	**Uniform**
Recruitment period-weights	**1 1 1 1 0 0**
Hazard ratios as entered (groups 1,2)	**1, 0.67**
Alpha	**0.025 (one-sided)**
Power (calculated)	**0.883**
Total sample size (designed)	**600**
Expected total number of events	**250**

c

ART – **A**NALYSIS OF **R**ESOURCES FOR **T**RIALS (version 1.1.0, 10 December 2013)

A sample size program by Abdel G Babiker, Patrick Royston & Friederike Barthel, MRC Clinical Trials Unit at UCL, London WC2B 6NH, UK.

Type of trial	**Superiority – time-to-event outcome**
Statistical test assumed	**Unweighted logrank test (local)**
Number of groups	**2**
Allocation ratio	**Equal group sizes**
Total number of periods	**5**
Length of each period	**One year**
Survival probs per period (group 1)	**0.555 0.542 0.536 0.518 0.506**
Survival probs per period (group 2)	**0.674 0.663 0.658 0.643 0.634**
Number of recruitment periods	**4**
Number of follow-up periods	**1**
Method of accrual	**Uniform**
Recruitment period-weights	**1 1 1 1 0**
Hazard ratios as entered (groups 1,2)	**1, 0.67**
Alpha	**0.025 (one-sided)**
Power (calculated)	**0.875**
Total sample size (designed)	**600**
Expected total number of events	**245**

d

ART – **A**NALYSIS OF **R**ESOURCES FOR **T**RIALS (version 1.1.0, 10 December 2013)

A sample size program by Abdel G Babiker, Patrick Royston & Friederike Barthel, MRC Clinical Trials Unit at UCL, London WC2B 6NH, UK.

Type of trial	**Superiority – time-to-event outcome**
Statistical test assumed	**Unweighted logrank test (local)**
Number of groups	**2**
Allocation ratio	**Equal group sizes**
Total number of periods	**4**
Length of each period	**One year**
Survival probs per period (group 1)	**0.555 0.542 0.536 0.518**
Survival probs per period (group 2)	**0.674 0.663 0.658 0.643**
Number of recruitment periods	**4**
Number of follow-up periods	**0**
Method of accrual	**Uniform**
Recruitment period-weights	**1 1 1 1**
Hazard ratios as entered (groups 1,2)	**1, 0.67**
Alpha	**0.025 (one-sided)**
Power (calculated)	**0.826**
Total sample size (designed)	**600**
Expected total number of events	**212**

Figure 5. Interim ART analysis plan

a

ART – ANALYSIS OF **R**ESOURCES FOR **T**RIALS (version 1.1.0, 10 December 2013)

A sample size program by Abdel G Babiker, Patrick Royston & Friederike Barthel, MRC Clinical Trials Unit at UCL, London WC2B 6NH, UK.

Type of trial	**Superiority – time-to-event outcome**
Statistical test assumed	**Unweighted logrank test (local)**
Number of groups	**2**
Allocation ratio	**Equal group sizes**
Total number of periods	**2**
Length of each period	**One year**
Survival probs per period (group 1)	**0.555 0.542**
Survival probs per period (group 2)	**0.674 0.663**
Number of recruitment periods	**2**
Number of follow-up periods	**0**
Method of accrual	**Uniform**
Recruitment period-weights	**1 1**
Hazard ratios as entered (groups 1,2)	**1, 0.67**
Alpha	**0.025 (one-sided)**
Power (calculated)	**0.471**
Total sample size (designed)	**300**
Expected total number of events	**91**

b

ART – ANALYSIS OF **R**ESOURCES FOR **T**RIALS (version 1.1.0, 10 December 2013)

A sample size program by Abdel G Babiker, Patrick Royston & Friederike Barthel, MRC Clinical Trials Unit at UCL, London WC2B 6NH, UK.

Type of trial	**Superiority – time-to-event outcome**
Statistical test assumed	**Unweighted logrank test (local)**
Number of groups	**2**
Allocation ratio	**Equal group sizes**
Total number of periods	**3**
Length of each period	**One year**
Survival probs per period (group 1)	**0.555 0.542 0.536**
Survival probs per period (group 2)	**0.674 0.663 0.658**
Number of recruitment periods	**3**
Number of follow-up periods	**0**
Method of accrual	**Uniform**
Recruitment period-weights	**1 1 1**
Hazard ratios as entered (groups 1,2)	**1, 0.67**
Alpha	**0.025 (one-sided)**
Power (calculated)	**0.684**
Total sample size (designed)	**450**
Expected total number of events	**151**

Figure 6. Final study design with 4 years of recruitment and 2 years of follow-up

ART – ANALYSIS OF **R**ESOURCES FOR **T**RIALS (version 1.1.0, 10 December 2013)

A sample size program by Abdel G Babiker, Patrick Royston & Friederike Barthel, MRC Clinical Trials Unit at UCL, London WC2B 6NH, UK.

Type of trial	**Superiority – time-to-event outcome**
Statistical test assumed	**Unweighted logrank test (local)**
Number of groups	**2**
Allocation ratio	**Equal group sizes**
Total number of periods	**6**
Length of each period	**One year**
Survival probs per period (group 1)	**0.555 0.542 0.536 0.518 0.506 0.506**
Survival probs per period (group 2)	**0.674 0.663 0.658 0.643 0.634 0.634**
Number of recruitment periods	**4**
Number of follow-up periods	**2**
Method of accrual	**Uniform**
Recruitment period-weights	**1 1 1 1 0 0**
Hazard ratios as entered (groups 1,2)	**1, 0.67**
Alpha	**0.025 (one-sided)**
Power (calculated)	**0.883**
Total sample size (designed)	**600**
Expected total number of events	**250**

Figure 7. Interim analysis

```
i.assign          _Iassign_1-2        (naturally coded; _Iassign_1 omitted)

         failure _d:  c == 1 2 3
   analysis time _t:  y/365.25
                 id:  pt_id

Iteration 0:   log likelihood = -406.31894
Iteration 1:   log likelihood = -405.71281
Iteration 2:   log likelihood = -405.71281
Refining estimates:
Iteration 0:   log likelihood = -405.71281

Stratified Cox regr. -- Breslow method for ties

No. of subjects =          298                 Number of obs    =         298
No. of failures =           89
Time at risk    =   228.109514
                                                LR chi2(1)       =        1.21
Log likelihood  =   -405.71281                  Prob > chi2      =      0.2709
```

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
_Iassign_2	.791492	.1684219	-1.10	0.272	.5215777	1.201086

Stratified by stage

Figure 8. GroupSeq result

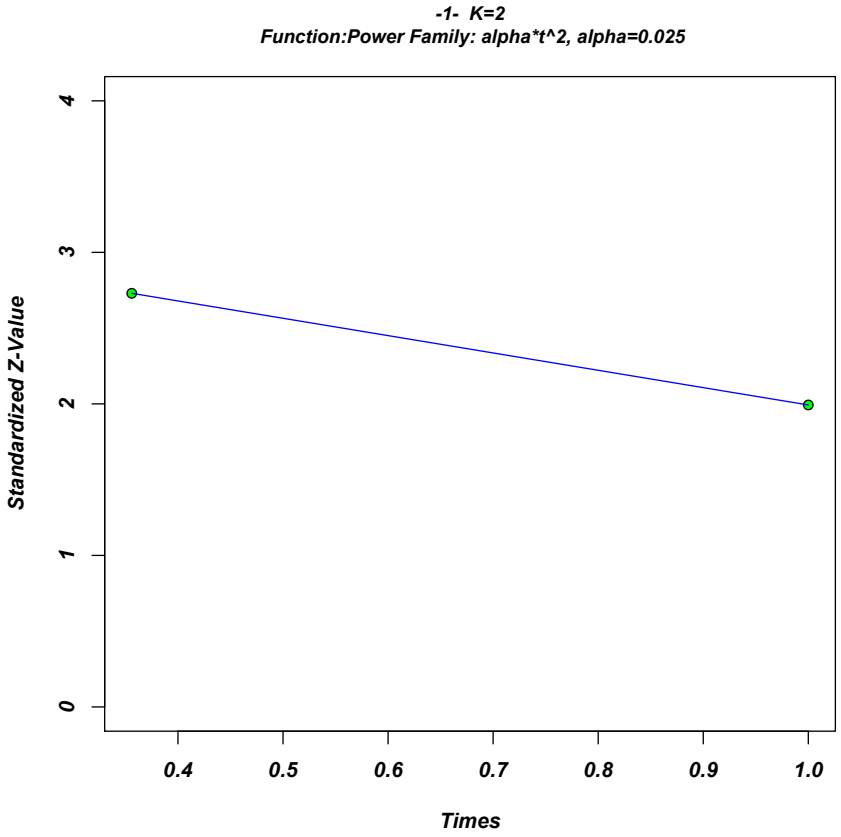

Figure 9. Final analysis

```
i.assign          _Iassign_1-2        (naturally coded; _Iassign_1 omitted)

         failure _d:  c == 1 2 3
   analysis time _t:  y/365.25
                 id:  pt_id

Iteration 0:   log likelihood = -1304.0967
Iteration 1:   log likelihood = -1301.5017
Iteration 2:   log likelihood = -1301.5017
Refining estimates:
Iteration 0:   log likelihood = -1301.5017

Stratified Cox regr. -- Breslow method for ties

No. of subjects =          589                 Number of obs    =         589
No. of failures =          241
Time at risk    =   1681.73306
                                               LR chi2(1)       =        5.19
Log likelihood  =   -1301.5017                 Prob > chi2      =      0.0227
```

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
_Iassign_2	.7451305	.0965423	-2.27	0.023	.5780256	.9605449

Stratified by stage

Figure 10. Effect on SMN

```
         failure _d:  c == 2
   analysis time _t:  y/365.25
                 id:  pt_id

Iteration 0:   log likelihood =  -20.44657
Iteration 1:   log likelihood = -20.445301
Iteration 2:   log likelihood = -20.445301
Refining estimates:
Iteration 0:   log likelihood = -20.445301

Stratified Cox regr. -- no ties

No. of subjects =          589                 Number of obs    =         589
No. of failures =            4
Time at risk    =   1681.73306
                                               LR chi2(1)       =        0.00
Log likelihood  =   -20.445301                 Prob > chi2      =      0.9598
```

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
2.assign	.9508616	.9510153	-0.05	0.960	.1338993	6.752373

Stratified by stage

Appendix

```
********** historical data **********

cd "/Users/chengliangdong/Google Drive/552/Coco_final"
use hep_proj_2015

gen long y=0
gen float c=0

replace c=1 if(date_rel<=last_cnt)
replace c=2 if(date_smn<date_dth | date_smn<date_rel)
replace c=3 if(date_dth<date_rel)

replace y=last_cnt if(c==0)
replace y=date_rel if(c==1)
replace y=date_smn if(c==2)
replace y=date_dth if(c==3)

label define c 0 "None" 1 "Recurrence" 2"SMN" 3 "Death"

stset y, failure(c==1,2,3) origin(time date_reg) scale(365.25)
id(ptnt_id)

sts list, at(0,0.5,1,1.5,2,2.5,3,3.5,4,4.5,5,5.5,6,6.5,7,7.5,8)
sts graph, ci

sts list, by(constg) at(0,1,2,3,4,5,6,7,8)
sts graph, by(constg) ci
sts test constg

net describe http://www.homepages.ucl.ac.uk/~ucakjpr/stata/art
net install art


artsurv, method(l) nperiod(8) ngroups(2) fp(0) edf0( 0.5549  0.5420
0.5356  0.5177  0.5062  0.5062  0.5062  0.5062 , ) hratio(1, 0.67)
alpha(0.025) power(0.8) aratios(1 1 ) recrt(3 0, 1, 0 ) distant(0)
detail(0) onesided(1) ni(0) tunit(1) trend(0)

artsurv, method(l) nperiod(8) ngroups(2) fp(0) edf0( 0.5549  0.5420
0.5356  0.5177  0.5062  0.5062  0.5062  0.5062 , ) hratio(1, 0.67)
alpha(0.025) power(0.8) aratios(1 1 ) recrt(4 0, 1, 0 ) distant(0)
detail(0) onesided(1) ni(0) tunit(1) trend(0)

artsurv, method(l) nperiod(8) ngroups(2) fp(0) edf0( 0.5549  0.5420
0.5356  0.5177  0.5062  0.5062  0.5062  0.5062 , ) hratio(1, 0.67)
alpha(0.025) power(0.8) aratios(1 1 ) recrt(5 0, 1, 0 ) distant(0)
detail(0) onesided(1) ni(0) tunit(1) trend(0)

artsurv, method(l) nperiod(8) ngroups(2) fp(0) edf0( 0.5549  0.5420
```

```
0.5356  0.5177  0.5062  0.5062  0.5062  0.5062 , ) hratio(1, 0.67)
alpha(0.025) power(0.8) aratios(1 1 ) recrt(6 0, 1, 0 ) distant(0)
detail(0) onesided(1) ni(0) tunit(1) trend(0)

** follow up

artsurv, method(l) nperiod(7) ngroups(2) fp(0) edf0( 0.5549  0.5420
0.5356  0.5177  0.5062  0.5062  0.5062  , ) hratio(1, 0.67)
alpha(0.025) n(600) aratios(1 1 ) recrt(4 0, 1, 0 ) distant(0)
detail(0) onesided(1) ni(0) tunit(1) trend(0)


artsurv, method(l) nperiod(6) ngroups(2) fp(0) edf0( 0.5549  0.5420
0.5356  0.5177  0.5062  0.5062   , ) hratio(1, 0.67) alpha(0.025)
n(600) aratios(1 1 ) recrt(4 0, 1, 0 ) distant(0) detail(0)
onesided(1) ni(0) tunit(1) trend(0)


artsurv, method(l) nperiod(5) ngroups(2) fp(0) edf0( 0.5549  0.5420
0.5356  0.5177  0.5062    , ) hratio(1, 0.67) alpha(0.025) n(600)
aratios(1 1 ) recrt(4 0, 1, 0 ) distant(0) detail(0) onesided(1) ni(0)
tunit(1) trend(0)


artsurv, method(l) nperiod(4) ngroups(2) fp(0) edf0( 0.5549  0.5420
0.5356  0.5177     , ) hratio(1, 0.67) alpha(0.025) n(600) aratios(1 1
) recrt(4 0, 1, 0 ) distant(0) detail(0) onesided(1) ni(0) tunit(1)
trend(0)


** interim
artsurv, method(l) nperiod(2) ngroups(2) fp(0) edf0( 0.5549  0.5420  ,
) hratio(1, 0.67) alpha(0.025) n(300) aratios(1 1 ) recrt(2 0, 1, 0 )
distant(0) detail(0) onesided(1) ni(0) tunit(1) trend(0)

artsurv, method(l) nperiod(3) ngroups(2) fp(0) edf0( 0.5549  0.5420
0.5356, ) hratio(1, 0.67) alpha(0.025) n(450) aratios(1 1 ) recrt(3 0,
1, 0 ) distant(0) detail(0) onesided(1) ni(0) tunit(1) trend(0)

** summary

artsurv, method(l) nperiod(6) ngroups(2) fp(0) edf0( 0.5549  0.5420
0.5356  0.5177  0.5062  0.5062   , ) hratio(1, 0.67) alpha(0.025)
n(600) aratios(1 1 ) recrt(4 0, 1, 0 ) distant(0) detail(0)
onesided(1) ni(0) tunit(1) trend(0)


********** interim **********

use cd_first_out,clear
```

```
gen long y=0
gen float c=0

replace c=1 if(time_rel<=time_lfp)
replace c=2 if(time_smn<time_dth | time_smn<time_rel)
replace c=3 if(time_dth<time_rel)

replace y=time_lfp if(c==0)
replace y=time_rel if(c==1)
replace y=time_smn if(c==2)
replace y=time_dth if(c==3)


label define c 0 "None" 1 "Relapse" 2"SMN" 3 "Death"

stset y, failure(c==1,2,3) scale(365.25) id(pt_id)

xi: stcox i.assign, strata(stage)

* bonus
gen comply=0
replace comply=1 if(assign==received)
tab comply


********************* final data ***********************

use cd_final,clear
drop if elig == 2

gen long y=0
gen float c=0

replace c=1 if(time_rel<=time_lfp)
replace c=2 if(time_smn<time_dth | time_smn<time_rel)
replace c=3 if(time_dth<time_rel)

replace y=time_lfp if(c==0)
replace y=time_rel if(c==1)
replace y=time_smn if(c==2)
replace y=time_dth if(c==3)


label define c 0 "None" 1 "Relapse" 2"SMN" 3 "Death"

stset y, failure(c==1,2,3) scale(365.25) id(pt_id)
xi: stcox i.assign, strata(stage) sch(sch)
```

```
gen comply=0
replace comply=1 if(assign==received)
tab comply

stset y, failure(c==2) scale(365.25) id(pt_id)
stcox i.assign, strata(stage)

* bonus
estat phtest
```