

1 **A Phase II Study of Amrubicin and Topotecan Combination Therapy in Patients**
2 **with Relapsed or Extensive-Disease Small-Cell Lung Cancer: Okayama Lung**
3 **Cancer Study Group Trial 0401**

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25 **Running Title:** Amrubicin and topotecan for SCLC

26 **Conflict of Interest:** none

27 **UMIN clinical trial registry:** C000000130

28 <https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&r>
29 [ecptno=R000000179&language=J](https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000000179&language=J)
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32 **Abstract**

33 **Backgrounds:** Chemotherapy is a mainstay in the treatment of extensive-disease
34 small-cell lung cancer (ED-SCLC), although the survival benefit remains modest. We
35 conducted a phase II trial of amrubicin (a topoisomerase II inhibitor) and topotecan (a
36 topoisomerase I inhibitor) in chemotherapy-naïve and relapsed SCLC patients.

37 **Methods:** Amrubicin ($35\text{mg}/\text{m}^2$) and topotecan ($0.75\text{mg}/\text{m}^2$) were administered on
38 days 3–5 and 1–5, respectively. The objective response rate (ORR) was set as the
39 primary endpoint, which was assessed separately in chemotherapy-naïve and relapsed
40 cases.

41 **Results:** Fifty-nine patients were enrolled (chemotherapy-naïve 31, relapsed 28). The
42 ORRs were 74% and 43% in the chemotherapy-naïve and relapsed cases, respectively.
43 Survival data were also promising, with a median progression-free survival time and
44 median survival time of 5.3 and 14.9 months and 4.7 and 10.2 months in the
45 chemotherapy-naïve and relapsed cases, respectively. Even refractory-relapsed cases
46 responded to the treatment favorably (27% ORR). The primary toxicity was
47 myelosuppression with grades 3 or 4 neutropenia in 97% of the patients, which led to
48 grades 3 or 4 febrile neutropenia in 41% of the patients and two toxic deaths.

49 **Conclusion:** This phase II study showed the favorable efficacy and moderate safety
50 profiles of a topotecan and amrubicin two-drug combination especially in relapsed
51 patients with ED-SCLC.

52

53 **Keywords:** lung cancer, topotecan, amrubicin

54

55 **1. Introduction**

56 The standard regimen for patients with extensive disease small-cell lung cancer
57 (ED-SCLC) has been cisplatin (CDDP)-based chemotherapy. Combination therapy with
58 etoposide (ETP) and CDDP or irinotecan and CDDP has been very effective in
59 previously untreated patients with ED-SCLC.^{1,2} However, the long-term survival rate is
60 low; early relapse occurs in the majority of responders, and salvage chemotherapy for
61 SCLC yields disappointing results.³ The survival of patients with ED-SCLC enrolled in
62 phase III trials has not improved significantly over the last two decades, clearly
63 suggesting the need for the further development of novel, more effective agents or
64 combination regimens.⁴

65 Recently, several novel agents have been developed with unique mechanisms of
66 action and have shown promise in the treatment of SCLC.⁵ One of them, amrubicin, is
67 an entirely synthetic anthracycline that inhibits DNA topoisomerase II activity. With an
68 overall response rate (ORR) of 78.8% and median survival time (MST) of 11.0 months,
69 amrubicin has demonstrated antitumor activity against previously untreated SCLC.⁶
70 Another novel agent, topotecan, is a semi-synthetic water-soluble analog of
71 camptothecin that inhibits DNA topoisomerase I activity. It, too, has shown favorable
72 antitumor activity against SCLC with an ORR of 39% and MST of 9.0 months.⁷
73 Previously, we conducted a phase I trial to determine the safety and efficacy of a
74 two-drug combination chemotherapeutic regimen of amrubicin and topotecan in patients
75 with untreated or relapsed ED-SCLC.⁸

76 Based on the results of the phase I trial, we conducted a phase II trial of
77 amrubicin and topotecan in patients with untreated or relapsed ED-SCLC to determine

78 the ORR primarily. Secondary objectives were to investigate toxicity, progression-free
79 survival (PFS), and overall survival.

80

81 **2. Materials and methods**

82 *2.1. Eligibility criteria*

83 Patients were recruited based on the following eligibility criteria: pathologically
84 proven SCLC; chemotherapy-naïve ED-SCLC defined as distant metastasis,
85 contralateral hilar lymph node metastasis or malignant pleural effusion,⁹ or relapsed
86 disease (one prior regimen allowed); Eastern Cooperative Oncology Group (ECOG)
87 performance status (PS) of 0 to 3; age ≤ 75 years; presence of measurable lesions; no
88 chemotherapy within 4 weeks before entry in the study; adequate hematological [white
89 blood cell (WBC) count $\geq 3000/\mu\text{L}$, neutrophil count $\geq 1500/\mu\text{L}$, hemoglobin level \geq
90 8.5 g/dL , platelet count $\geq 10 \times 10^4/\mu\text{L}$], renal (serum creatinine level $\leq 1.5 \text{ mg/dL}$), and
91 hepatic (total bilirubin level $\leq 1.5 \text{ mg/dL}$, serum transaminases $\leq 2.5 \times$ upper limit of
92 normal range) function; and adequate pulmonary reserves [arterial oxygen pressure
93 (PaO_2) $\geq 60 \text{ Torr}$]. Relapsed cases included those with sensitive relapse (an interval of
94 at least 90 days after the completion of first-line chemotherapy) and
95 chemotherapy-refractory relapse (no response to first-line chemotherapy or relapse
96 within 90 days after the completion of first-line chemotherapy). Patients with
97 symptomatic brain metastasis, double cancer, massive effusion requiring drainage, or
98 severe comorbidities (*e.g.*, uncontrolled diabetes, heart disease, infectious disease, or
99 pulmonary fibrosis) were ineligible. Pretreatment evaluations included a complete
100 history, physical examination, laboratory tests, chest radiography, electrocardiography,
101 computed tomography (CT) of the chest and abdomen, magnetic resonance imaging

102 (MRI) of the brain, and a radionuclide bone scan. Staging was conducted according to
103 the tumor, node, metastasis system.¹⁰ Positron emission tomography (PET)/CT was also
104 used for staging in some cases.

105 All patients gave written consent, and the protocol was approved by the
106 institutional review board of each participating institute and performed in accordance
107 with the amended 2000 version of the World Medical Association's Declaration of
108 Helsinki.

109

110 2.2. *Treatment scheme*

111 The doses and schedules of both agents were based on phase I trial results.⁸
112 Topotecan was diluted in 100 mL of physiological saline and administered
113 intravenously as a 1-h infusion at a dose of 0.75 mg/m² on days 1 through 5. After
114 completing the topotecan infusion, amrubicin was diluted in 20 mL of physiological
115 saline and administered intravenously as a 5-min bolus injection at a dose of 35 mg/m²
116 on days 3 through 5. Each patient was pre-medicated with intravenous dexamethasone
117 and granisetron.

118 The treatment was repeated every four weeks for up to four cycles unless disease
119 progression or unacceptable toxicity was observed, or the patient refused further
120 treatment. Initiation of the next cycle of chemotherapy was delayed until the WBC and
121 platelet count recovered to $\geq 3000/\mu\text{L}$ and $\geq 10 \times 10^4/\mu\text{L}$, respectively, and
122 non-hematologic toxicities resolved to \leq grade 1. Patients were permitted to receive any
123 other chemotherapy for SCLC after completing or discontinuing the regimen. If
124 hematological toxicity of grade 4 lasting more than 4 days or non-hematological
125 toxicity \geq grade 3 was observed in a prior cycle, the amrubicin dose was reduced each

126 cycle by 5 mg/m². The protocol treatment was stopped if patients developed the same
127 toxicities after the second dose reduction. If grade 4 leukopenia, grade 4 neutropenia, or
128 febrile neutropenia was observed, use of granulocyte colony-stimulating factor (G-CSF)
129 was permitted.

130

131 *2.3. Assessment of antitumor activity and toxicity*

132 Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 guidelines
133 were applied to evaluate responses. Patients were evaluated for SCLC, with tumor
134 assessments at baseline every two cycles, and at the end of treatment. The best overall
135 response was defined as the best response recorded from the start of treatment until
136 disease progression or recurrence. Complete and partial responses were confirmed by
137 two observations no less than 4 weeks apart. A determination of stable disease required
138 disease stabilization for at least 6 weeks. In this study, we also defined the disease
139 control rate (DCR) as the proportion of patients with complete and partial responses and
140 stable disease.¹¹ All toxicities were graded according to the National Cancer Institute
141 Common Terminology Criteria for Adverse Events v3.0. Patients were monitored
142 closely for signs of cardiotoxicity during the study, and an electrocardiogram was
143 required at the start of treatment.

144

145 *2.4. Statistical Analysis*

146 The primary endpoint of this study was the overall response rate (ORR), and
147 secondary end points were PFS, overall survival, and the toxicity profile. The efficacy
148 of topotecan and amrubicin combination therapy was assessed separately for
149 chemotherapy-naïve and relapsed patients. For chemo-naïve cases, assuming that a 90%

150 ORR in eligible patients would indicate potential usefulness, whereas a 70% ORR
151 would constitute the lower limit of interest, with $\alpha = 0.10$ and $\beta = 0.10$, the estimated
152 accrual was 25 patients. For relapsed cases, assuming that a 30% ORR would indicate
153 potential usefulness, whereas a 10% ORR would constitute the lower limit of interest,
154 with $\alpha = 0.10$ and $\beta = 0.10$, the estimated accrual was also 25 patients. This regimen was
155 to be rejected when < 12 and < 2 of the first 16 cases had an ORR at the interim analysis,
156 for the chemotherapy-naïve and salvage cases, respectively. With an assumed 10%
157 dropout rate, the number of patients needed was 28 each. Overall survival was defined
158 as the interval between the date of enrollment in this study and death or the last
159 follow-up visit. PFS was defined as the interval between the date of enrollment and the
160 date of the first observation of disease progression or death from any cause. The
161 survival distribution was estimated using the Kaplan-Meier method. All statistical
162 analyses were conducted with STATA/SE version 10.0 software (College Station, TX).

163

164 **3. Results**

165 *Patient characteristics and treatment delivery*

166 A total of 59 consecutive patients with 31 chemotherapy-naïve or 28 relapsed
167 ED-SCLC were enrolled from eight institutions. Their demographics are shown in
168 Table 1. All patients were assessable for efficacy and safety. The median number of
169 treatment cycles was four (range 1–7 cycles) and three (range 1–8 cycles) in the
170 chemotherapy-naïve and relapsed cases, respectively. Among patients who received
171 only three or less cycles of treatment, the most common reason for treatment cessation,
172 was disease progression (15 of the 29 patients). At the time of analysis, 29 of 31 (94%)
173 chemotherapy-naïve and 24 of 28 (86%) relapsed patients developed disease

174 progression. Of these, 26 chemotherapy-naïve and 11 relapsed patients received salvage
175 chemotherapies: platinum-based doublet (n = 19), non-platinum-based doublet (n = 5),
176 and monotherapy (n = 2) in the chemotherapy-naïve patients, and platinum-based
177 doublet (n = 4), non-platinum doublet (n = 1), and monotherapy (n = 6) in the relapsed
178 patients.

179

180 *Response*

181 Due to early febrile neutropenia-related death (day 20, cycle 1), one patient
182 received no formal response assessment. The planned interim analysis revealed this
183 regimen had potent activity (13 and 6 responders) and the committee decided to
184 continue further patient accrual in the chemotherapy-naïve and salvage settings,
185 respectively. The ORR of chemotherapy-naïve patients was 74% (95% confidence
186 interval (CI) 55–88%). This did not satisfy the initial setting of the lower limit of
187 interest (70%), and thus the primary endpoint was not met for this population. By
188 contrast, 43% of relapsed patients responded to the study treatment (95% CI 24–63%),
189 which clearly met the lower limit of interest (10%).

190 In 28 relapsed patients, the ORR and DCR were 53% and 82%, respectively, for
191 the sensitive-relapsed cases, and 27% and 82%, respectively, for the refractory-relapsed
192 cases (Table 2).

193

194 *Survival*

195 All the patients were assessable for the survival analysis. At the time of this
196 analysis (January, 2010), 11 patients were still alive, and median follow-up time was
197 43.2 months ranging from 4.3 to 75.9 months. The median PFS time was 5.3 months for

198 the chemotherapy-naïve cases and 4.7 months for relapsed cases (Table 3 and Figure 1).
199 The overall median survival time (MST) was 14.9 and 10.2 months for the
200 chemotherapy-naïve and relapsed cases, respectively. When relapsed cases were
201 classified by the type of relapse pattern, the median progression-free survival was 5.8
202 months in patients with sensitive relapse and 3.3 months in patients with refractory
203 relapse. The overall median survival time was 10.2 and 10.5 months in sensitive and
204 refractory relapse, respectively (Figure 2).

205

206 *Safety*

207 Adverse events of grade 3 or worse are listed in Table 4. Myelosuppression was
208 the primary adverse event. Grades 3 and 4 neutropenia, thrombocytopenia, and anemia
209 were observed in 97%, 51%, and 42% of the patients, respectively. Median duration of
210 neutropenia was five days. G-CSF was administered in 50 patients (85%), whereas 14
211 patients received blood transfusion. Grade 3 or worse non-hematological toxicities
212 including anthracycline-related cardiac toxicities were relatively mild, except for febrile
213 neutropenia, which resulted in two treatment-related deaths (chemo-naïve setting and
214 refractory relapsed setting in one each).

215

216 **4. Discussion**

217 In this relatively small study, the combination of amrubicin and topotecan
218 yielded an ORR of 74% and 43% in the chemotherapy-naïve and relapsed cases,
219 respectively. The survival data were also promising with a median PFS time and MST
220 of 5.3 and 14.9 months and 4.7 and 10.2 months in the chemotherapy-naïve and
221 relapsed cases, respectively. Even refractory-relapsed cases responded to this treatment

222 (27% ORR). The major observed toxicity was myelosuppression. Grades 3 and 4
223 neutropenia occurred in 97% of the patients, resulting in grades 3 and 4 febrile
224 neutropenia in 41% of the patients.

225 In a first-line setting, platinum plus irinotecan or etoposide is considered a
226 standard treatment for ED-SCLC and approved in Japan. These regimens produce an
227 ORR of 68 to 84%, a median PFS of 4.8 to 6.9 months, and a MST of 9.4 to 12.8
228 months.¹ Combination therapy consisting of cisplatin plus topotecan or cisplatin plus
229 amrubicin has also been evaluated and has similar effects (56 to 88% ORR, 7.0-month
230 median PFS, and 10.3 to 13.6 month-MST).^{12,13} In this study, combination therapy of
231 topotecan and amrubicin produced less favorable efficacy than we initially expected
232 although it yielded a nearly identical efficacy with a 74% ORR, 5.3-month median PFS,
233 and 14.9 month-MST.

234 With regard to relapsed patients, Inoue *et al.* conducted a randomized phase II
235 trial of amrubicin versus topotecan for relapsed SCLC patients and reported an ORR of
236 38% and 13% in amrubicin monotherapy and topotecan monotherapy, respectively.¹⁴
237 The respective median PFS times and MSTs were 3.5 and 8.1 months (amrubicin
238 monotherapy) and 2.2 and 8.4 months (topotecan monotherapy). Based on our *post-hoc*
239 sub-analysis stratifying relapse type, the efficacy of the amrubicin and topotecan
240 combination therapy seemed more favorable especially in the refractory-relapsed cases
241 when compared simply with each single therapy (27% vs. 0–17% ORR, 82% vs.
242 18–68% DCR, 3.3 vs. 1.5–2.6-month median PFS, and 10.5 vs. 5.3-5.4-month MST).¹⁴
243 Another trial also showed somewhat lower response rate of amrubicin monotherapy for
244 refractory cases.¹⁵ This might suggest some synergistic effects of the two drugs despite
245 the need for further investigations.

246 As for the toxicity profiles, neutropenia in our combination therapy was mainly
247 moderate, which parallels that in our prior phase I trial.⁸ The occurrence of neutropenia
248 in 83-93% of the patients undergoing amrubicin monotherapy^{14,16,17} and 87% of the
249 patients undergoing topotecan monotherapy¹⁴ seemed also similar to our findings.
250 Furthermore, as in monotherapy, non-hematological toxicities other than febrile
251 neutropenia of the amrubicin and topotecan combination therapy were generally
252 tolerable. However, thrombocytopenia, anemia, febrile neutropenia and two toxic deaths
253 seemed more severe in the combination therapy than the monotherapy^{6,14,15}, suggesting
254 the need for cautious administration of the doublet therapy.

255 We have several limitations. Since this was an exploratory phase II single-arm
256 trial, some selection bias is possible, and a simple comparison between our results and
257 historical clinical data would be unwarranted and inconclusive. A prospective
258 comparative study is clearly required. Also, this study design mixes up 3 populations of
259 patients (untreated, relapsed-sensitive, and relapsed-refractory). Since only 59 patients
260 enrolled, interpretation of the results is limited by the 3 small subsets of patients. The
261 two populations of relapsed patients should have been stratified prospectively.
262 Furthermore, we accrued PS3 patients as well as PS 0-2 patients in this study according
263 to the previous clinical trial designs^{18,19}. However, to date, this inclusion criterion has
264 been unusual in most clinical trials, and the great majority of patients accrued in this
265 study had indeed an excellent PS (0 or 1 in 93%). Thus, the efficacy and safety for PS
266 2-3 pts would still remain unclear.

267

268 **5. Conclusions**

269 In conclusion, this phase II study showed the favorable efficacy and moderate
270 safety profiles of a topotecan and amrubicin two-drug combination especially in
271 relapsed patients with ED-SCLC, while this regimen was less effective in the first-line
272 setting and not worth while further being evaluated.

273

274 **Conflict of Interest**

275 None declared.

276

277 **Acknowledgment**

278 We thank the Okayama Lung Cancer Study Group members for their dedication and
279 cooperation throughout the course of this work. The authors are also deeply grateful for
280 all of the participants who made this study possible.

281

282 **Contributors**

283 KH, KK, and HU were involved in the conception and design of the study. NN, KH, SK,
284 KK, NT, KC, TS, DK, SH, AT, SH, and MT were involved in the provision of study
285 material, patients, and data acquisition. KH, KK and NT were involved in data analysis
286 and interpretation. All authors were involved in writing the report and approved the
287 final version.

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360 **All table & figure captions**

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362 Table 1 Demographics of the patients (n = 59)

363

364 Table 2 Subset analysis of efficacy stratified by the type of relapse

365

366 Table 3 Objective response and survival

367

368 Table 4 Adverse events (grade 3 or worse)

369

370 **Figure 1.** Overall (solid) and progression-free (dotted) survival curves

371 A, chemotherapy-naïve patients; B, relapsed patients

372

373 **Figure 2.** Overall (solid) and progression-free (dotted) survival curves

374 A, sensitive-relapsed patients; B, refractory-relapsed patients

375

1 Table 1 Demographics of the patients (n = 59)

	Chemo-naïve (n=31)	Relapsed (n=28)
Age, median (range), years	67 (52-75)	69 (54-73)
Gender (M / F)	28 / 3	24 / 4
ECOG PS (0 / 1 / 2)	3 / 26 / 2	11 / 15 / 2
Smoking history (current / former / never)	11 / 15 / 2	16 / 12 / 3
Prior irinotecan use	-	7
Prior etoposide use	-	21
Type of treatment setting		
sensitive relapse	-	17
refractory relapse	-	11

2 Sensitive relapse (at ≥ 90 days after completion of first-line chemotherapy).
3 Chemotherapy-refractory relapse (no response to first-line chemotherapy or relapse
4 within 90 days after completing first-line chemotherapy). Abbreviations: ECOG PS =
5 Eastern Cooperative Oncology Group performance status.
6

7 Table 2 Subset analysis of efficacy stratified by the type of relapse

	Sensitive relapse (n=17)		Refractory relapse (n=11)	
	No.	%	No.	%
Response				
complete response	0	0	0	0
partial response	9	53	3	27
stable disease	5	29	6	55
progressive disease	2	12	2	18
inevaluable	1*	6	-	-
Overall response rate	9	53	3	27
Disease control rate	14	82	9	82
Survival				
median PFS (months)	5.8		3.3	
median OS (months)	10.2		10.5	
1-yr OS (95%CI; %)	38.2 (15.9–60.5)		18.2 (2.9–44.2)	

8 **Early death. Abbreviations: PFS = progression-free survival, OS = overall survival,

9 CI = confidence interval.

10

11 Table 3 Objective response and survival

Response	Chemo-naïve (n=31)		Relapsed (n=28)	
	No.	%	No.	%
complete response	1	3	0	0
partial response	22	71	12	43
stable disease	6	19	11	39
progressive disease	2	6	4	14
inevaluable	-	-	1*	3
Overall response rate	23	74	12	43
(95% CI)		(55 to 88)		(24 to 63)
Disease control rate	29	94	23	82
Survival				
median PFS (months)	5.3		4.7	
median OS (months)	14.9		10.2	
1-yr OS (95% CI; %)	68.4 (47.8–82.3)		29.9 (14.3–47.4)	

12 *Early death. Abbreviations: PFS = progression-free survival, OS = overall survival, CI =

13 confidence interval.

14

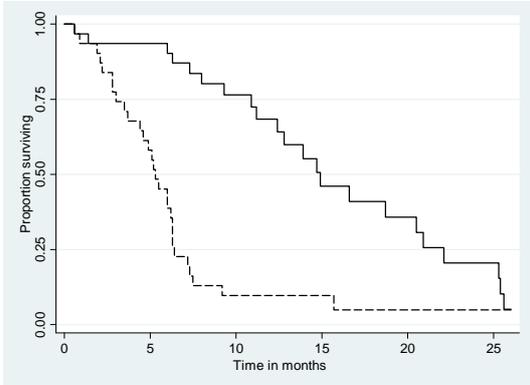
15 Table 4 Adverse events (grade 3 or worse)

	Grade 3	Grade 4	≥Grade 3(%)
Hematologic			
neutropenia	10	47	97
thrombocytopenia	15	15	51
anemia	21	4	42
Non-hematologic			
fatigue	2	3	9
febrile neutropenia	20	4	41
nausea/vomiting	2	1	5
diarrhea	0	1	2
pneumonitis	1	1	3
ileus	0	1	2

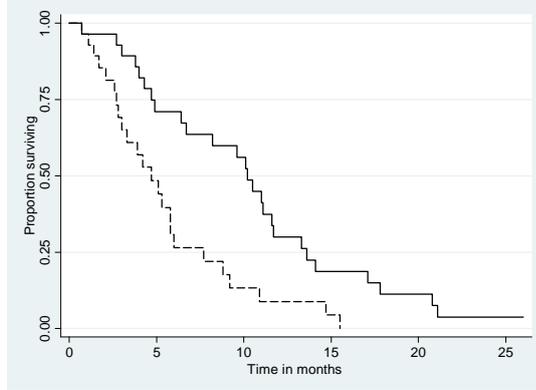
16

1 **Figure 1**

2 **A**



B

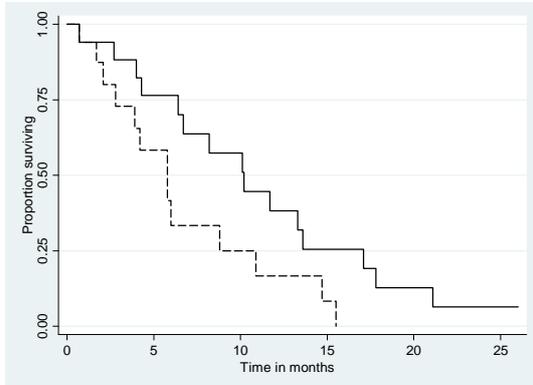


3

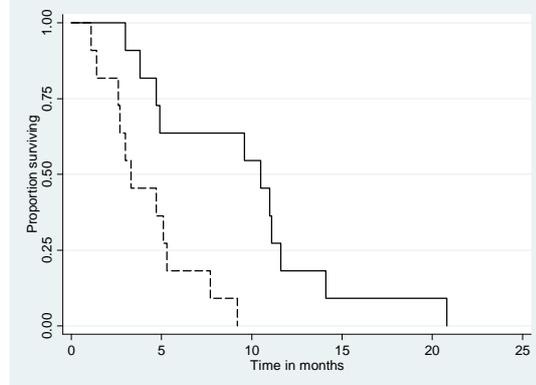
4

5 Figure 2

6 A



B



7