



Low ATM expression and progression-free and overall survival in advanced gastric cancer patients treated with first-line XELOX chemotherapy

Samuel J. Klempner^{1,2#}, Munveer S. Bhangoo^{3#}, Hubert Y. Luu⁴, Seung Tae Kim⁵, Joseph Chao⁶, Kyoung-Mee Kim⁷, Jeeyun Lee⁵

¹The Angeles Clinic and Research Institute, Los Angeles, CA, USA; ²Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA; ³Division of Hematology Oncology, Scripps Clinic, La Jolla, CA, USA; ⁴Department of Surgery, University of California, San Francisco, CA, USA; ⁵Department of Medicine, Samsung Medical Center, Seoul, Korea; ⁶Department of Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA; ⁷Department of Pathology and Translational Genomics, Samsung Medical Center, Seoul, Korea

Contributions: (I) Conception and design: SJ Klempner, MS Bhangoo, J Lee; (II) Administrative support: J Lee; (III) Provision of study materials or patients: ST Kim, KM Kim; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Samuel J. Klempner, MD. Director of Precision Medicine and GI Oncology, The Angeles Clinic and Research Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA. Email: sklempner@theangelesclinic.org.

Background: Gastric cancer (GC) is a leading cause of cancer-specific mortality with limited biologically informed treatments. The ataxia telangiectasia mutated (*ATM*) gene is critically involved in the repair of double-stranded DNA breaks and a component of DNA damage repair (DDR) pathways. Platinum salts are hypothesized to have increased efficacy in tumors deficient in DDR pathways. We sought to investigate an association between ATM status and response to XELOX in a homogenous first line GC patient cohort.

Methods: A clinically annotated cohort of 137 Korean patients with advanced GC treated with first-line XELOX was retrospectively examined for ATM status by immunohistochemistry. Correlation between ATM expression and clinicopathologic variables was performed by two-tailed, unpaired *t*-tests and Fisher's exact tests. Kaplan-Meier survival analysis curves and Cox proportional hazards models were used to evaluate for independent predictors of disease-free survival (DFS) and overall survival (OS).

Results: Low ATM expression was observed in 19.0% (26/137) of patients and was not associated with clinicopathologic features or response rate to XELOX. Univariate, but not multivariable, logistic regression and Cox analysis identified ATM as an independent risk factor influencing OS and DFS. A higher ECOG score independently predicted worse survival [hazard ratio (HR) 2.96, P=0.016] and complete surgical resection independently protected against progression of disease (HR 0.69, P=0.007).

Conclusions: Low ATM expression was not associated with increased response rates to XELOX in a single-institution cohort of advanced GC patients. Similarly, ATM status did not predict DFS or OS after platinum-based chemotherapy.

Keywords: Stomach cancer; ataxia telangiectasia mutated (ATM); DNA damage; PARP; platinum

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Introduction

Gastric adenocarcinoma is a leading cause of cancer-related death globally (1). Although considerable progress has been made in the molecular classification of gastric cancer (GC), the prognosis remains poor with overall survival (OS) ranging from 10 to 16 months in metastatic disease (2-5). Evidence-based targeted approaches based on specific molecular profiles are limited to HER2 amplified and a small subset of microsatellite instable (MSI)-high tumors (6). There exists considerable unmet need for predictive biomarkers to guide the rational use of existing therapies and to identify novel therapeutic approaches or combinations.

Acquired defects in DNA damage repair (DDR) pathways are a defining mechanism of tumorigenesis (7). Both germline and somatic mutations in DDR genes are not only associated with increased risk of the development of cancer but also represent attractive targets for therapeutic intervention. The ataxia telangiectasia mutated (*ATM*) gene is critically involved in the repair of double-stranded DNA breaks. Specifically, *ATM* localizes to sites of double-stranded DNA breaks and interacts with *BRCA1* (breast cancer type 1) and 53BP1 (p53-binding protein) (8). *ATM* affects multiple downstream pathways activating DNA-damage repair along with cell-cycle arrest and apoptosis (9).

Platinum salts are hypothesized to have increased efficacy in DDR-deficient tumors. Mechanistically, platinum drugs induce double-strand DNA breaks which selectively leads to unsustainable levels of genomic instability resulting in tumor cell death. In DDR-defective cells the impaired repair machinery is believed to underlie the synthetic lethality after treatment with platinum compounds. Patients with *BRCA1*- and *BRCA2*-mutated breast, ovarian, and prostate cancer appear to exhibit increased responsiveness to platinum-based chemotherapy (10).

Low expression of *ATM* in GC is associated with poorly-differentiated histology, lymph node involvement, and worse overall 5-year survival among patients undergoing curative surgical resection (11). Pre-clinical models have suggested increased sensitivity of *ATM* deficient cells to inhibition with olaparib and SN-38 though platinum associations remain understudied (12). Recently, the phase III GOLD trial failed to show a survival benefit for olaparib in unselected advanced GC progressing after first-line therapy. This lack of benefit was seen in both the overall study population as well as patients with tumors expressing low levels of *ATM* (13).

Whether or not deficiencies in *ATM* are associated with increased tumor response and survival in patients with GC treated with platinum chemotherapy is currently unknown. Identifying molecularly defined GC patient subgroups who are more, or less, likely to benefit from a given approach is an ongoing need in GC. We sought to explore the relationship between outcomes and *ATM* status in a homogenous cohort of Korean patients with advanced GC treated with first-line capecitabine in combination with oxaliplatin (XELOX).

Methods

Patients

We retrospectively reviewed patients with advanced GC (unresectable stage 3 or stage 4) at Samsung Medical Center (Seoul, Korea) from 2013 to 2017. All patients received first-line (1L) capecitabine and oxaliplatin (XELOX) at standard dosing. Data was abstracted from medical records including sex, age at diagnosis, performance status. The study was approved by the institutional review board at Samsung Medical Center and all data was stored securely (2015-10-062). Pathologic features including pathologic subtype, anatomic site, and HER2/neu status were collected. Outcomes data included tumor response, and the date of progression or death.

Immunohistochemistry (IHC)

Tumor sections (2 mm in diameter) were obtained from formalin-fixed paraffin-embedded biopsy samples. Tissue was arranged in new recipient paraffin block (tissue array block) utilizing a trephine apparatus (Superbiochips Laboratories, Seoul, Korea) as previously reported (14). Immunohistochemical staining was performed using an automatic immunostainer (DAKO, Glostrup, Denmark) according to the manufacturer's instructions. The primary antibody used was anti-*ATM* antibody [Y170]. Low-expression of *ATM* (ATM_{low}) was defined as greater than 50% loss of nuclear staining.

Statistics

Descriptive statistics were reported as proportions and means. Correlation between *ATM* expression and clinicopathologic variables were performed by two-tailed, unpaired *t*-tests and Fisher's exact tests. Treatment outcomes

included overall response rate (ORR), progression-free survival (PFS), and OS. PFS was defined as the date of first chemotherapy to the date of cancer progression, death from any cause or the date of last follow-up visit. OS was defined as the date of first chemotherapy to the date of death from any cause and was censored at the date of the last follow-up visit. Independent variables were selected a priori for analysis in multivariable logistic regression. Kaplan-Meier survival analysis was used to compare disease-free survival (DFS) and OS; the log-rank test was used to determine statistical significance. Cox proportional hazards modeling was used to assess the impact of individual risk factors on length of survival or time to progression of disease. Variables with observed P values <0.05 were considered statistically significant for this analysis, and 95% CI were calculated. All statistical analyses were performed using STATA 15.0 (STATACorp LLC, College Station, Texas, USA).

Results

Clinicopathologic features

Baseline characteristics (n=137) are presented in *Table 1*. The mean age of all patients was 55.7 years (range, 26–80 years). Fifty-one patients (37.2%) were female. The most common histologic subtypes by WHO classification were poorly-differentiated adenocarcinoma (n=68, 49.6%), signet ring adenocarcinoma (n=29, 21.2%), and moderately differentiated adenocarcinoma (n=28, 20.4%). The primary tumors include gastric body (n=73, 53.3%), antrum (n=41, 29.9%), cardia (n=16, 11.7%), other (n=6, 4.4%). One-hundred and thirty-two (96.4%) patients had ECOG status of 0 or 1. HER2/neu overexpression was absent in 130/135 patients (96.3%) (*Table 1*).

Outcomes of patients with ATM_{loss} vs. ATM_{intact}

Among the 137 patients analyzed for ATM expression, 26 (19.0%) exhibited low or undetectable ATM expression by IHC (*Figure 1, Table 1*). Unadjusted univariate analysis demonstrated an association between ATM_{low} status and ECOG status (P=0.046) and prior surgery (P=0.041). All other clinicopathologic variables showed no association with ATM expression. Multivariable logistic regression was performed including the variables age, sex, ECOG status, WHO classification, HER2 status, performance of surgical resection, primary tumor location, stage, and ATM status. Advanced ECOG status was independently associated with

worse OS [odds ratio (OR) 4.83; 95% CI: 1.58–14.78, P=0.006, *Table 2*]. This was also seen on Kaplan-Meier survival analysis (*Figure S1*).

Oncologic response to XELOX based on ATM expression

All patients analyzed received capecitabine plus oxaliplatin as 1L systemic therapy for advanced gastric adenocarcinoma. The mean number of cycles received was 7.1 (range, 1–23). The ORR across the entire cohort was 31.4%, composed entirely of partial responses (*Table 3*). The ORR for ATM_{low} was 26.9% compared with 32.4% in among patients with ATM_{intact} status, not statistically significant (P=0.800). The median PFS for the overall study population was 6.12 months (*Figure 2A*), consistent with prior 1L trials (2). The median OS for the study population was 10.1 months (*Figure 2B*). Among all 137 patients, 53 deaths (39%) occurred in the follow-up period. Crude analysis based on Kaplan-Meier curves showed no difference in survival outcomes for patients with ATM_{low} versus ATM_{intact} patients in both OS and PFS (*Figure 2C,D*).

Univariate and multivariable Cox models

In our univariate Cox model patients with an ECOG higher than 1 had significantly increased risk of death compared to those with ECOG 1 or lower. Patients who underwent a curative surgical resection (either total or subtotal gastrectomy) had significantly decreased risk of recurrence over the analysis period. These findings were robust in multivariable Cox analysis both ECOG [hazard ratio (HR) 2.80; P=0.02, 95% CI: 1.19–6.60, *Table 4*] and for prior curative resection (HR 0.69; P=0.007, 95% CI: 0.52–0.90, *Table 4*). ATM status was not significantly associated with OS or PFS in the multivariable-adjusted Cox model.

Discussion

Deficient ATM expression was identified in 1/5 of advanced Korean GC patients but was not associated with improved outcomes with 1L XELOX. The incidence of low or absent ATM expression in our population is consistent with prior reports. A large retrospective cohort of ATM expression in GC tumors revealed low ATM expression in 22% of cases, consistent between primary and metastatic tumor samples (15).

Deleterious genomic alterations involving *ATM* occur in 10 percent of GC (16). The discordance in the frequency of gene alterations compared with protein expression (as

Table 1 Baseline characteristics of 137 Korean patients with advanced GC treated with first-line XELOX

Clinicopathologic feature	Overall	ATM		P value
		ATM _{low} (n=26)	ATM _{intact} (n=111)	
Age, mean (SD)	55.7 (11.9)	59.7 (10.3)	54.8 (12.1)	0.900
Sex, female (%)	51 (37.2)	10 (38.5)	41 (36.9)	0.890
ECOG				0.046
0	24 (17.5)	3 (11.5)	21 (18.9)	
1	108 (78.8)	20 (76.9)	88 (79.3)	
2	5 (3.6)	3 (11.5)	2 (1.8)	
WHO diagnosis, n (%)				0.670
Well-differentiated adeno	3 (2.2)	0	3 (2.7)	
Moderately-differentiated adeno	28 (20.4)	7 (26.9)	21 (18.9)	
Poorly-differentiated adeno	68 (49.6)	13 [50]	55 (49.5)	
Signet ring adeno	29 (21.2)	5 (19.2)	24 (21.6)	
Papillary adeno	6 (4.4)	0	6 (5.4)	
Others	3 (2.2)	1 (3.8)	2 (1.8)	
Primary tumor location, n (%)				0.560
Body	73 (53.3)	14 (53.8)	59 (53.2)	
Antrum	41 (29.9)	9 (34.6)	32 (28.8)	
Cardia	16 (11.7)	1 (3.8)	15 (13.5)	
Fundus	1 (0.7)	0 (0)	1 (0.9)	
Other	6 (4.4)	2 (7.7)	4 (3.6)	
HER2 status, n (%)				0.970
Intact	130 (96.3)	25 (96.2)	105 (96.3)	
Overexpressed/amplified	5 (3.8)	1 (3.8)	4 (3.7)	
Prior surgery, n (%)				0.041
Total gastrectomy	22 (16.2)	3 (11.5)	19 (17.3)	
Subtotal gastrectomy	24 (17.6)	9 (34.6)	15 (13.6)	
None	90 (66.2)	14 (53.9)	76 (69.1)	
Stage, n (%)				0.150
1	1 (0.8)	0 (0)	1 (1.0)	
2b	1 (0.8)	1 (4.0)	0 (0)	
3c	6 (4.6)	2 (8.0)	4 (3.8)	
4	122 (93.8)	22 (88.0)	100 (95.2)	
Xeloda cycles received, mean (SD)	7.1 (4.0)	6.9 (3.8)	7.1 (4.1)	0.420

GC, gastric cancer; XELOX, capecitabine in combination with oxaliplatin.

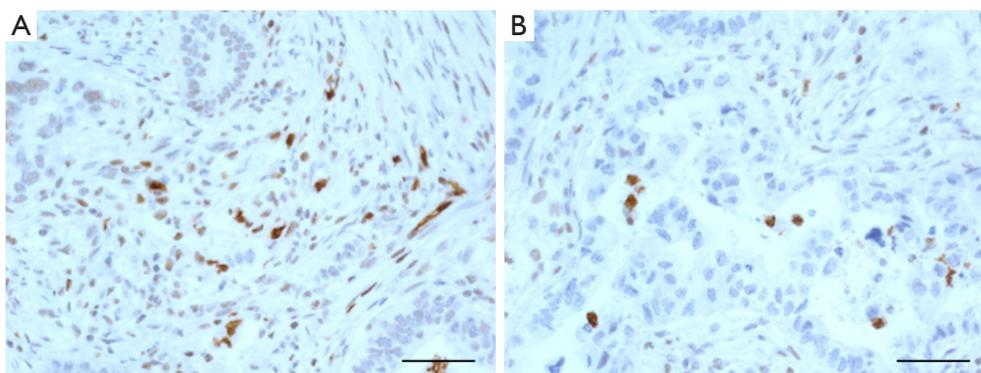


Figure 1 Representative IHC demonstrating ATM intact (A) and ATM loss in 70% tumor cells (B) at 400× magnification (scale bar =50 μm).

Table 2 Multivariable logistic regression analysis in a cohort of GC patients treated with 1L XELOX

Variables	OR	95% CI	P value
Age	1.01	0.98–1.05	0.450
Sex	1.10	0.47–2.57	0.820
ECOG	4.83	1.58–14.78	0.006
WHO	0.93	0.67–1.29	0.660
HER2 status	1.21	0.18–8.02	0.840
Surgical resection	0.94	0.55–1.59	0.810
Tumor location	1.05	0.72–1.52	0.800
Stage	1.04	0.37–2.94	0.950
ATM status	0.47	0.16–1.35	0.160

GC, gastric cancer; OR, odds ratio; 1L, first line; XELOX, capecitabine in combination with oxaliplatin; ATM, ataxia telangiectasia mutated.

measured by IHC) may be a consequence of non-genomic changes affecting protein expression. Our approach was not oriented to study the genomic context of ATM loss though further investigation is warranted, however, the apparent mutual exclusivity of ATM loss and HER2 amplification from TCGA data is noted and confirmed in our cohort.

The data presented here represent the first report of 1L outcomes in advanced GC patients treated with platinum-chemotherapy and stratified by ATM expression. In this cohort, no difference was observed in terms of response rates to platinum-based chemotherapy between ATM_{low} and ATM_{intact} patients. Our results may be somewhat confounded by the uniform Asian population which tends toward improved outcomes in several prior trial datasets (17).

Table 3 Response characteristics of 137 Korean patients treated with XELOX and assessed for ATM expression

Clinical outcome	ATM _{low} , n (%)	ATM _{intact} , n (%)	P value
Complete response	0	0	0.8
Partial response	7 (26.9)	36 (32.4)	
Stable disease	15 (57.7)	62 (55.9)	
Progressive disease	4 (15.4)	13 (11.7)	
Disease control rate	22 (84.6)	98 (88.3)	

XELOX, capecitabine in combination with oxaliplatin; ATM, ataxia telangiectasia mutated.

However, the homogenous population (single Korean institution) studied here may be considered both a strength and weakness, and external validation in non-Asian patients is important. While we acknowledge the relatively small sample size to our knowledge this remains the largest reported cohort. The retrospective nature of this analysis also is an inherent limitation.

The clinical significance of aberrant homologous recombination repair pathways defined by genomic alteration or deficient protein expression in predicting response to platinum-based chemotherapy is an area of ongoing clinical interest. Pre-clinical models have demonstrated the importance of both BRCA1 and BRCA2 in assembly of the Rad51 complex which is essential to the repair of double-stranded DNA breaks (18,19). Patients with BRCA-associated ovarian cancer demonstrate improved survival versus those non-BRCA mutated tumors. One mechanism for improved outcomes may be increased sensitivity to platinum-based chemotherapy (10,20). Similar associations between alterations in BRCA1 and BRCA2 and

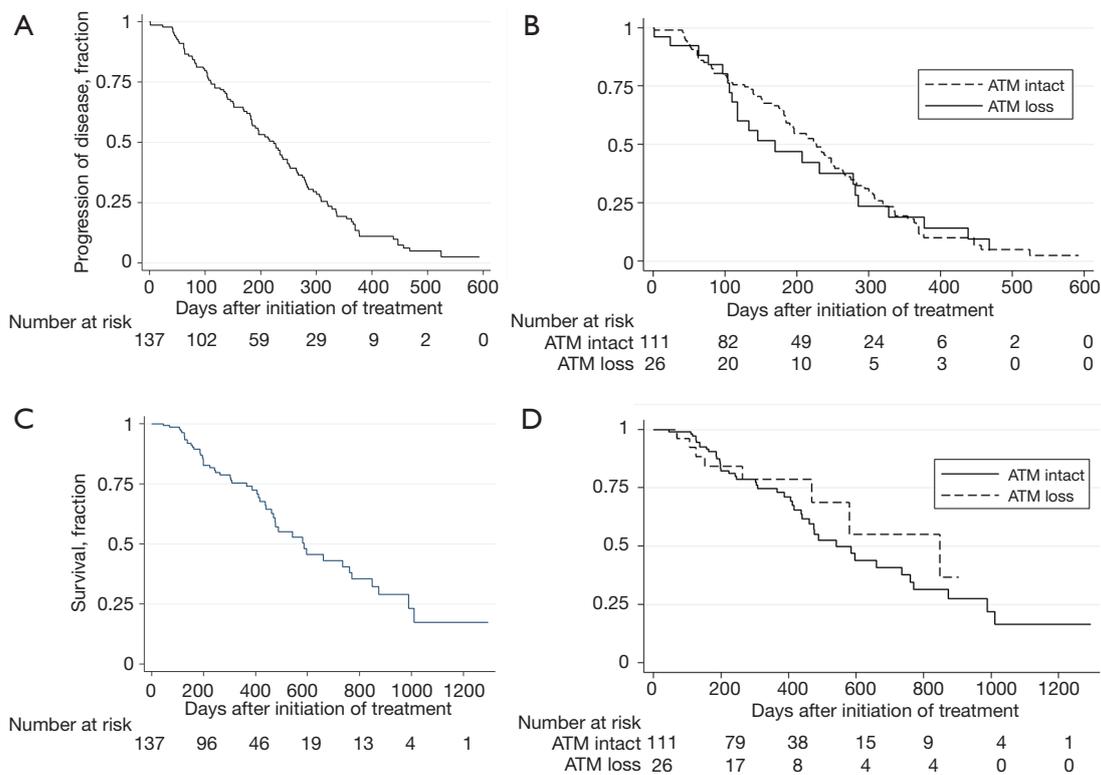


Figure 2 GC outcomes with 1L XELOX. (A,B) Progression-free survival for all patients (A) and stratified by ATM status (B); (C,D) overall survival for all patients (C) and stratified by ATM status (D). GC, gastric cancer; 1L, first line; ATM, ataxia telangiectasia mutated; XELOX, capecitabine in combination with oxaliplatin.

Table 4 Multivariate Cox proportional hazard analysis of OS and PFS in a cohort of GC patients treated with 1L XELOX and assessed for ATM expression

Variables	Overall survival			Progression-free survival		
	HR	95% CI	P value	HR	95% CI	P value
Age	0.99	0.97–1.02	0.980	0.99	0.98–1.02	0.990
Sex	1.05	0.56–1.94	0.890	0.92	0.57–1.48	0.740
ECOG	2.80	1.19–6.60	0.019	1.49	0.90–2.45	0.120
WHO	1.15	0.91–1.47	0.240	1.18	1.00–1.40	0.054
HER2	1.69	0.40–7.21	0.480	0.39	0.14–1.12	0.080
Surgical resection	1.14	0.78–1.67	0.510	0.69	0.52–0.90	0.007
ATM status	0.66	0.30–1.47	0.310	1.49	0.88–2.50	0.140

OS, overall survival; PFS, progression-free survival; 1L, first line; GC, gastric cancer; XELOX, capecitabine in combination with oxaliplatin; ATM, ataxia telangiectasia mutated.

platinum-sensitivity are seen in breast and prostate cancer (10,21,22).

Mechanistically, alterations in ATM are predicted to interfere with homologous recombination repair and, therefore, potentially serve as a predictive biomarker for DNA-damaging therapies. In pre-clinical models, the significance of ATM defects has been variably demonstrated to be associated with increased sensitivity to platinum chemotherapy. One study of ATM-deficiency in mammary cells demonstrated increased sensitivity to DNA-damaging agents (23). Yet, two other pre-clinical reports have failed to consistently demonstrate the significance of ATM in predicting platinum-sensitivity (24,25). Mutations in genes involved in homologous recombination repair including *BRCA1*, *BRCA2*, *PALB2*, *ATM* confer clinical benefit to PARP inhibition across multiple tumor types (26-29). Deficiencies in ATM were hypothesized to be associated with response to PARP inhibition in patients with GC. The phase 3 GOLD study randomized patients with advanced, previously treated GC, to weekly paclitaxel plus or minus olaparib (13). The study failed to improve OS in the overall study population or in patients with ATM-low tumors. Notably, the inclusion criteria for this study required prior therapy with a platinum-containing regimen; however, the time interval between progression after platinum chemotherapy and study enrollment was highly variable. Another open question surrounds whether under-dosing of olaparib to accommodate chemotherapy may have compromised optimal inhibition of PARP. An association between initial response to platinum chemotherapy and subsequent sensitivity to PARP-inhibition is currently not known.

Future studies require defining optimal cutoffs for low ATM expression. Immune checkpoint inhibitors now available for advanced GC pose interesting combinatorial strategies (30,31). Recent preclinical studies have implicated ATM as being required for inducing PD-L1 expression in response to radiation-induced cellular DNA damage (32). Whether deficiency in ATM and its apparent linkage to impairing adaptive immune resistance mechanisms translates into improved outcomes for patients receiving combination of platinum and immune checkpoint agents needs further study. Examining tumor ATM expression from patient specimens in such ongoing trials is of interest.

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Footnote

Conflicts of Interest: SJ Klempner receives research funding (institutional) from LEAP therapeutics and Astellas and has served as a consultant/advisor for Lilly Oncology, Astellas, Boston Biomedical and Foundation Medicine. J Chao receives research funding from Merck (institutional) and has served as a consultant/advisor for Merck, Boston Biomedical, and Five Prime Therapeutics. The remaining authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by Samsung Medical Center (IRB 2015-10-062) and informed consent was taken from all patients.

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Supplementary

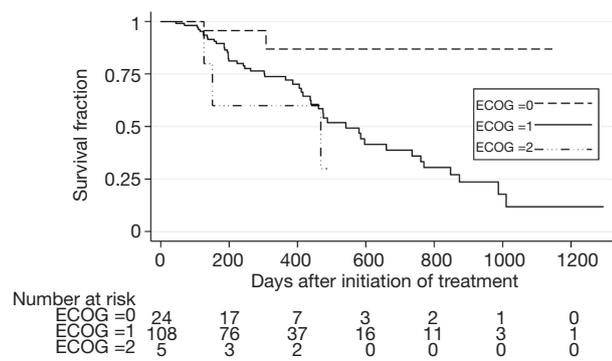


Figure S1 Overall survival by ECOG status in 1L XELOX therapy for advanced GC. 1L, first line; GC, gastric cancer; XELOX, capecitabine in combination with oxaliplatin.