Original Article

Title: Analysis of Esophago-Gastric Cancer Patients Enrolled in the National Cancer Institute –Cancer Therapy Evaluation Program -Sponsored Phase 1 Trials

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Running Title: Phase 1 analysis for Esophago-Gastric Cancer

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Background: In phase 1 trials, an important entry criterion is life expectancy predicted to be more than 90 days, which is generally difficult to predict. The Royal Marsden Hospital (RMH) prognostic score that is determined by LDH level, albumin level, and number of metastatic sites of disease was developed to help project patient outcomes. At the moment, there have been no systematic analyses to evaluate the utility of RMH score for esophago-gastric cancer (EGC) patients.

Methods: All non-pediatric phase 1 oncology trials sponsored by the National Cancer Institute-Cancer Therapy Evaluation Program that began between 2001 and 2013 were considered in this review.

Results: Of 4722 patients with solid tumors, 115 patients were eligible for our analysis; 54 (47%) of esophagus, 14 (12%) of esopago-gastric junction and 47 (41%) of stomach cancer. 86 (75%) patients had good (0-1) and 29 (25%) had poor (2-3) RMH score. Disease control rates were significantly different between patients with good and poor RMH score (49% vs. 17%; 2-side Fisher's exact test P=0.004). The median treatment duration and OS for good and poor RMH patients were significantly different, (median treatment duration: 2.1 months vs. 1.2 months, respectively, P=0.016; median OS: 10.9 months vs. 2.1 months, respectively, P<0.001). In the multivariate analysis, age (≥60), ECOG PS (≥2) and the RMH score (2-3) were significant predictors of poor survival.

Conclusions: The RMH score is a strong tool to predict the prognosis of EGC patients who might participate in a phase 1 trial.

(244 words)

Mini abstract:

The Royal Marsden Hospital score can be used as a strong tool to predict the prognosis of patients with esophago-gastric cancer who will participate in phase 1 trials. (27 words)

Key words: phase 1 trials; esophago-gastric cancer; National Cancer Institute (NCI); Cancer Therapy Evaluation Program (CTEP); the Royal Marsden Hospital prognostic score

Introduction

Esophageal and gastric cancers are, respectively, the eighth and fifth most common malignancies in the world [1]. In 2012, an estimated 456,000 and 951,000 new cases of esophageal and stomach cancer, respectively, occurred worldwide. Both diseases often present in advanced stages because of late onset of symptoms and, due to the limited availability of effective treatment strategies, are associated with poor survival. Thus, approximately 400,000 and 723,000 deaths from esophageal and gastric cancer, respectively, occurred in 2012 [1].

The majority of esophageal cancers worldwide are squamous cell carcinoma (SCC) or adenocarcinoma in origin. While the incidence of SCC decreased in the United States, the incidence of adenocarcinoma stemming from Barrett's esophagus has been increasing dramatically [2]. Similarly, the incidence of adenocarcinoma of the esophago-gastric junction (EGJ) and proximal stomach have increased, while the incidence of distal gastric carcinoma has declined [3].

The incidence of gastric cancer varies with different geographic regions. Rates are highest in Eastern Asia, Eastern Europe, and South America, while the lowest rates are in North America and parts of Africa [1]. Furthermore, as the worldwide incidence of gastric cancer has declined, especially in North America and Western Europe, gastric

cancer has become less common in the United States [4].

Patients with unresectable and recurrent esophago-gastric cancer (EGC) at time of diagnosis are usually treated with systemic chemotherapy. At present, fluoropyrimidine and platinum-based chemotherapy with or without trastuzumab, an anti–HER2 antibody, are globally regarded as standard first-line chemotherapy for esophago-gastric adenocarcinoma [5, 6]. Recently, owing to randomized studies, taxanes, irinotecan, and ramucirumab, an anti-Vascular Endothelial Growth Factor Receptor -2 antibody, have been regarded as standard second-line therapeutic options [7-11]. However, the prognosis of patients with advanced or recurrent EGC remains poor with a median overall survival (OS) of only 12 months.

When patients do not respond to conventional systemic chemotherapy but have a good performance status (PS), they are often candidates for clinical trials. Phase 1 trials are designed primarily to evaluate the tolerability and toxicity profile of new therapies and to determine the recommended phase 2 dose. The generally accepted inclusion and exclusion criteria for these trials include adequate organ function and reasonable PS in order to ensure safety and avoid unnecessary toxicity. The life expectancy predicted to be less than 90 days is also used for excluding patients with poor prognosis although this is notoriously difficult to predict. There have been various

analyses to identify the variables to detect poor prognosis. Recently, the Royal Marsden Hospital (RMH) prognosis score was developed to help predict the outcomes of patient on phase 1 trials. From the multivariate analysis of the RMH phase 1 data set, LDH level, albumin level, and number of metastatic sites of disease were selected as significantly poorer prognostic factors [12]. The RMH prognostic score has also been validated using various prospectively and retrospectively selected cohorts [13, 14].

The Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI), in the United States, coordinates and supports the largest, publicly funded oncology clinical trials program in the world. NCI-CTEP is currently supporting 180 phase 1 clinical trials. NCI-CTEP also manages and provides about 100 investigational new drugs (INDs) for CTEP-sponsored clinical trials.

At present, there have been few analyses of clinical benefits and prognoses for EGC patients who were registered in phase 1 trials [15, 16]. Those analyses assessed the toxicities, treatment-related trial discontinuations, and efficacies. However, the impact of phase 1 treatment on safety and efficacy for patients with EGC has not yet been evaluated in a large population. Although the prognostic variables for overall survival have been analyzed [15], the usefulness of the RMH prognostic score for EGC patients has not yet been evaluated.

In this analysis, we retrospectively investigated the characteristics and clinical benefits in patients who participated in CTEP-sponsored phase 1 clinical trials. We also investigated whether the RMH score is a useful tool to predict the prognosis of EGC patients who might participate in phase 1 trials.

Methods

Patient Eligibility:

All non-pediatric phase 1 oncology trials sponsored by NCI-CTEP, initiated between 2001 and 2013, involving enrolled patients with EGC, were analyzed in this study. These trials were conducted at the National Institutes of Health (NIH) Clinical Center and other academic institutions around the United States. In this analysis, we excluded phase 1/2 trials.

Data were provided from the Clinical Trials Monitoring System (CTMS) database, which is managed by Theradex Systems® (Princeton, NJ). The CTMS database is prospectively maintained, with robust data management and auditing practices [17]. We received the anonymized clinical data, containing type of trials, patients' characteristics, safety profiles, and clinical efficacies as in the previous reports [18].

The Royal Marsden Hospital (RMH) prognostic score:

The RMH score was determined by 3 variables: LDH level, albumin level, and number of metastatic sites of disease. LDH values greater than the upper limit of normal, albumin level <3.5 g/dL, and number of metastatic sites >2, each received 1 point. A total score of 0 or 1 indicates a good prognosis, whereas a total score of 2 or 3 denotes a poor prognosis [12].

Endpoints and Statistical Methods:

All statistical evaluations were performed by the primary investigator and our statistician (HB and LR). Summary statistics of patient characteristics were provided; Kaplan-Meier product limit estimates were used to generate curves for treatment duration and overall survival (OS). Treatment duration was defined as the time from start of phase 1 treatment to time of discontinuation as judged by the investigator, due to objective or clinical disease progression, intolerable toxicities, or death. OS was defined as the time from the start of phase 1 treatment to death or last date patient was known to be alive. For OS, patients were censored at the time of their last follow-up if they were still alive. Responses in phase 1 studies were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.0 or RECIST ver. 1.1.

Fisher's exact test was used to compare the differences of the toxicities, response rate and disease control rate among the groups with different RMH scores. A log-rank test was used to assess the differences in treatment duration and OS among the groups with different RMH prognostic scores. Univariate and multivariate Cox proportional hazards models were fit to test the covariate effect on OS. Age, sex, tumor location, ECOG PS, hemoglobin value, platelet count, LDH level, albumin level, the number of metastatic sites, RMH score, and number of previous treatments were included in an initial multivariate Cox proportional hazards model. A forward selection method model was also used. Covariates with $P < 0.05$ were retained in the model.

All analyses were carried out using IBM SPSS version 21.0 software (IBM, Tokyo, Japan). All reported P values were for 2-sided tests, and $P < 0.05$ was considered statistically significant.

Results:

Patient Characteristics:

Data from 186 CTEP phase 1 trials conducted between February 2001 and July 2013 were included in this analysis. A total of 4722 patients were enrolled in these trials and 126 (2.7%) patients had EGC. Eleven cases were omitted for analyses because

insufficient clinical data were available (type of trial, patient characteristics, safety profiles, clinical effects, etc.). Thus, the study researchers analyzed 115 patients with EGC from 44 CTEP phase 1 studies.

Eighty-four (73.0%) patients were men and the median patient age was 59 years (range, 30-85 years). Most patients were Caucasian (77.4%; *N*=89). Fifty four (47%) cancer cases were located in the esophagus, 14 (12%) were in the EGJ, and 47 (41%) were in the stomach. The most common pathologic subtype was adenocarcinoma (89.6%; *N*=103). Twenty-six (22.6%) patients had ECOG performance status (PS) 0, eighty-four (73.0%) patients had PS 1, and five (4.3%) patients had PS 2. The median number of prior treatments was 4 (range, 0-13). Forty-two (36.5%) and 31 (27.0%) patients received prior surgery and radiation, respectively. Of 115 eligible patients, 86 (75%) patients had good (0-1) RMH score and 29 (25%) had poor (2-3) RMH score (Table 1).

Treatments:

Of 44 CTEP phase 1 studies, 17 were with single agents (3 chemotherapy only and 14 biologic agent only) and 27 were with combination therapy (10 biologic combination and 17 biologic + chemotherapy).

Thirty-two (28%) of 115 patients were treated with a single agent and 83 (72%) with combination therapy. Of 32 patients treated with a single agent, 8 (7%) were treated with a cytotoxic agent, and 24 (21%) with a biologic therapy. Of 83 patients treated with combination therapy, 18 (16%) were treated with biologic agent combination therapy, and 65 (56%) with biologic and cytotoxic agents (Table 2).

Safety:

Among 115 patients, 87 patients (75.7%) experienced grade 3 or 4 toxic events; these events included 29 with neutropenia, 13 with thrombocytopenia, 12 with diarrhea, 10 with nausea, and 8 with vomiting. However, only 1 (0.9%) grade 5 event was observed in this analysis. When we counted dose limiting toxicity (DLT) events, 21 cases were observed (10 blood system disorders, 5 general disorders, 5 gastrointestinal disorders, and 1 cardiac disorder) (Table 3).

Although there were trends that higher toxicities occurred in patients with poor RMH score, we did not observe statistical significance either for grade 3–4 toxic events (2-sided P=0.142 by Fisher's exact test) or for DLT events (2-sided P=0.406 by Fisher's exact test) between patients with good versus poor RMH score (Table 3).

Response:

Of 86 patients with good RMH score, 7 (8%) partial response (PR) and 35 (41%) stable disease (SD) cases were reported (response rate: 8%, disease control rate: 49%). On the other hand, of 29 patients with poor RMH score, only 1 (3%) PR and 4 (14%) SD cases were reported (response rate: 3%, disease control rate: 17%). Response rates for patients with good versus poor RMH scores (8% vs. 3%) were not significantly different (2-sided P=0.68 by Fisher's exact test), whereas disease control rates for good versus poor RMH patients (49% vs 17%) were significantly different (2-sided P=0.004 by Fisher's exact test) (Table 4).

Treatment Duration and Overall Survival:

The log-rank analysis showed that patients with a good (0-1) RMH score had a median treatment duration of 2.1 months (95% CI, 1.7-2.4 months) vs. those with a poor (2-3) RMH score, who had a median treatment duration of 1.2 months (95% CI, 1.0-1.4), a statistically significant difference (P=0.016) (Figure 1A).

The median OS of patients with a good (0-1) RMH score was 10.9 months (95% CI, 8.1-13.7 months) while for those with a poor (2-3) RMH score, it was 2.1 months (95% CI, 1.3-2.8), which also was a statistically significant difference by the log-rank analysis

(*P*<0.0001) (Figure 1B).

Prognostic Value of the RMH Score:

In the univariate Cox proportional hazards model of OS, ECOG PS (0 or 1 vs. 2; *P*<0.0001), LDH level (≤upper limit of normal (ULN) vs. >ULN; *P*<0.0001), albumin level (≥3.5g/dl vs. <3.5g/dl; *P*<0.0001), and RMH scores (poor vs. good; *P*<0.0001) were significantly associated with a poor phase 1 clinical trial OS (Table 5). In the multivariate analysis with RMH score, but not including its components (LDH level, albumin level, and number of metastatic sites of disease), RMH score (poor vs. good; *P*<0.0001; HR=0.294), Age (60> vs. ≥60; *P*=0.046; HR=0.562), and ECOG PS (0-1 vs. 2; *P*=0.019; HR=0.214) were significantly associated with a poor OS (Table 5).

Discussion:

We comprehensively reviewed phase 1 oncology trials sponsored by NCI-CTEP between 2001 and 2013 and investigated the characteristics and clinical benefits in enrolled patients with EGC. Of 4722 patients with solid tumor, we found only 126 (2.7%) patients with EGC. This suggests that EGC is a minor component of NCI-CTEP-sponsored phase 1 trials in the United States when compared with that of

East Asian countries [16].

Because the main NCI-CTEP-sponsored phase 1 trials use combination therapies under CTEP-INDs which completed a dose-finding phase 1 trial as single agent, the combination therapies with biologic agents (Biologic combination or Biologic + Chemotherapy) were the majority (total 72%) of phase 1 trials for EGC.

In this analysis, 18.3% of patients with EGC had DLTs and 75.7% had grade 3 or 4 toxicities. The 75.7% with grade 3 or 4 toxicities is considerably higher than reported by previous analyses (19.7% to 39%) [15, 16]. A reasonable explanation is that the main NCI-CTEP-sponsored phase 1 trials for EGC were for combinations with biologic and cytotoxic agents. Actually, 27 patients received combinations with cisplatin, irinotecan, and CDK9 kinase inhibitor and 7 received combinations with FOLFIRI and CDK9 kinase inhibitor. Those treatment regimens are expected to yield a high level of hematological toxicities. On the other hand, grade 5 toxicities were rare (0.9%).

Despite the finding that an expected survival >3 months is frequently one of the eligibility criteria for enrollment in most phase 1 trials, clinicians who screen patients often fail to accurately predict individual survival profiles, and as many as 15% to 20% of these patients die within the first 3 months of phase 1 trial entry [19]. In our analysis, the median OS of patients with good RMH scores and poor RMH scores were 10.9

months and 2.1 months, respectively; this was a statistically significant difference in the log-rank analysis (P<0.0001). The 2.1 months of median OS for patients with poor RMH scores was shorter than the 3 months major entry criterion. In the multivariate analysis, RMH score was also significantly associated with a poor OS. The significant difference in OS between patients with good and poor RMH score was also consistent in the separate age groups (60> years old: median OS 9.9 months vs. 1.9 months, P=0.001; 60≤ years old: 11.2 months vs. 2.7 months, P=0.004).

Our analysis has some limitations. We retrospectively used the CTMS database to analyze patient characteristics, treatment duration, and OS since we could not access the medical records of each patient. Since most CTEP-sponsored phase 1 clinical trials do not consistently capture the date of death when patients go off study, this information was only captured for 52 (45%) patients. Since the patients with good RMH scores tended to live longer than those with poor RMH scores, date of death was captured less for the former (41%) than for the latter (66%). While it is possible that this introduced statistical bias into the calculations of the predictive value of the RMH score for OS, it is very unlikely that it significantly affected the results.

In conclusion, the RMH prognostic score could be a strong tool for predicting the prognosis of EGC patients who will participate in a phase 1 trial. The median OS of 2.1

months for EGC patients with a poor RMH score also suggests that these patients should not be included in phase 1 clinical trials.

(2429 words)

Legends for figures:

Figure 1: Kaplan-Meier plots of Treatment duration and Overall survival for patients with good and poor Royal Marsden Hospital (RMH) prognosis score

Figure 1A: The median treatment duration of patients with a good (0-1) RMH score (*N*=86) and a poor (2-3) RMH score (*N*=29) were respectively 2.1 months (95% CI, 1.7-2.4) and 1.2 months (95% CI, 1.0-1.4), which was a statistically significant difference by the log-rank analysis (*P*=0.016). **Figure 1B**: The median OS of patients with a good RMH score was 10.9 months (95% CI, 8.1-13.7 months) while for those with a poor RMH score, it was 2.1 months (95% CI, 1.3-2.8), which also was a statistically significant difference by the log-rank analysis (*P*<0.0001).

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Disclosure:

The authors have declared no conflicts of interest.

Ethical Standards:

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. We analyzed the delinked anonymous data extracted from the Clinical Trials Monitoring Branch (CTMB) database, which is prospectively managed and closely audited by Theradex® Systems (Princeton,NJ) in collaboration with National Cancer Institute (NCI). Hideaki Bando received the ethical training managed by NCI before accessing the database.

Reference:

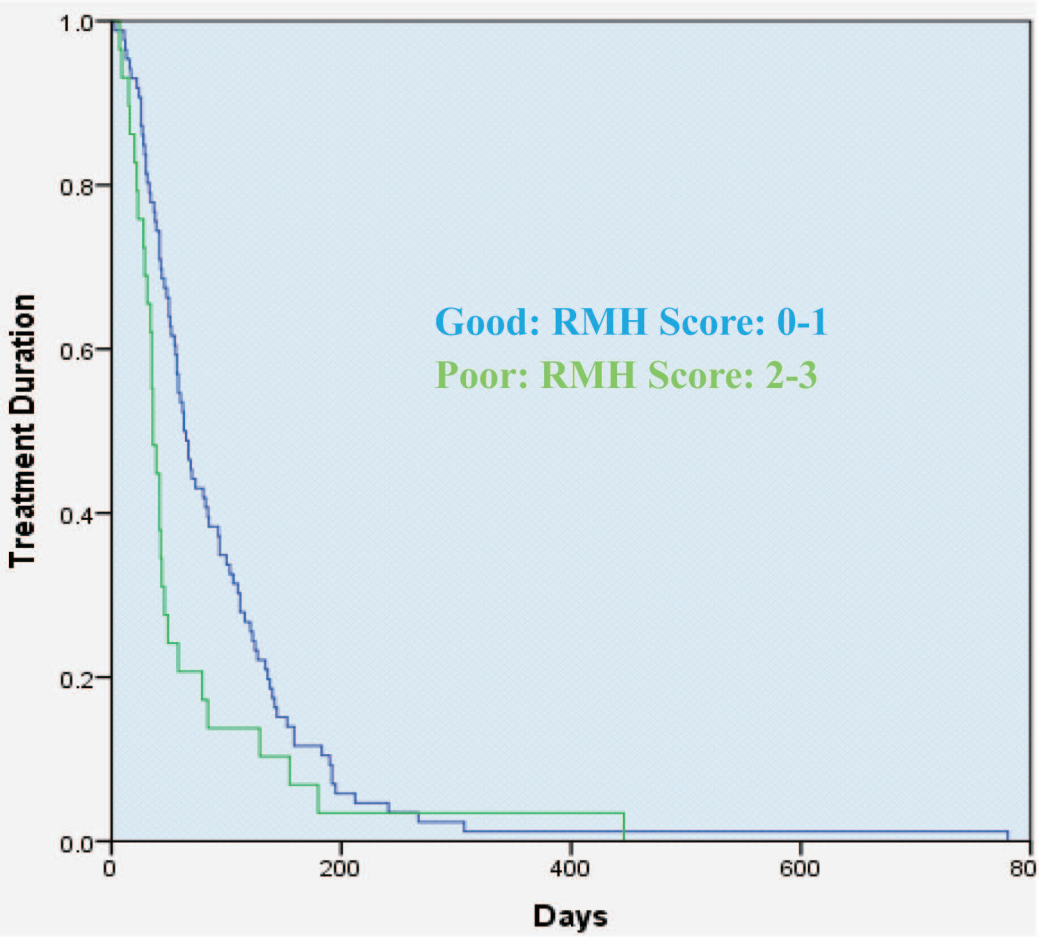
1. Ferlay, J., et al., *Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012.* Int J Cancer, 2015. **136**(5): p. E359-86.
2. Pohl, H., B. Sirovich, and H.G. Welch, *Esophageal adenocarcinoma incidence: are we reaching the peak?* Cancer Epidemiol Biomarkers Prev, 2010. **19**(6): p. 1468-70.
3. Salvon-Harman, J.C., et al., *Shifting proportions of gastric adenocarcinomas.* Arch Surg, 1994. **129**(4): p. 381-8; discussion 388-9.
4. Siegel, R., D. Naishadham, and A. Jemal, *Cancer statistics, 2013.* CA Cancer J Clin, 2013. **63**(1): p. 11-30.
5. Bang, Y.J., et al., *Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial.* Lancet, 2010. **376**(9742): p. 687-97.
6. Kang, Y.K., et al., *Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial.* Ann Oncol, 2009. **20**(4): p. 666-73.
7. Kang, J.H., et al., *Salvage Chemotherapy for Pretreated Gastric Cancer: A Randomized Phase III Trial Comparing Chemotherapy Plus Best Supportive Care With Best Supportive Care Alone.* J Clin Oncol, 2012.
8. Fuchs, C.S., et al., *Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial.* Lancet, 2014. **383**(9911): p. 31-9.
9. Wilke, H., et al., *Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial.* Lancet Oncol, 2014. **15**(11): p. 1224-35.
10. Ford, H.E., et al., *Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial.* Lancet Oncol, 2014. **15**(1): p. 78-86.
11. Thuss-Patience, P.C., et al., *Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer--a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO).* Eur J Cancer, 2011. **47**(15): p. 2306-14.
12. Arkenau, H.T., et al., *Clinical outcome and prognostic factors for patients treated*

within the context of a phase I study: the Royal Marsden Hospital experience. Br J Cancer, 2008. **98**(6): p. 1029-33.

13. Arkenau, H.T., et al., *Prospective validation of a prognostic score to improve patient selection for oncology phase I trials.* J Clin Oncol, 2009. **27**(16): p. 2692-6.
14. Garrido-Laguna, I., et al., *Validation of the Royal Marsden Hospital prognostic score in patients treated in the Phase I Clinical Trials Program at the MD Anderson Cancer Center.* Cancer, 2012. **118**(5): p. 1422-8.
15. Khan, K., et al., *Phase I trials in patients with relapsed, advanced upper gastrointestinal carcinomas: experience in a specialist unit.* Gastric Cancer, 2014. **17**(4): p. 621-9.
16. Kawazoe, A., et al., *Clinical outcomes in 66 patients with advanced gastric cancer treated in phase I trials: the NCCHE experience.* Invest New Drugs, 2015.
17. Ansher, S.S. and R. Scharf, *The Cancer Therapy Evaluation Program (CTEP) at the National Cancer Institute: industry collaborations in new agent development.* Ann N Y Acad Sci, 2001. **949**: p. 333-40.
18. Hyman, D.M., et al., *Nomogram to predict cycle-one serious drug-related toxicity in phase I oncology trials.* J Clin Oncol, 2014. **32**(6): p. 519-26.
19. Arkenau, H.T., et al., *90-Days mortality rate in patients treated within the context of a phase-I trial: how should we identify patients who should not go on trial?* Eur J Cancer, 2008. **44**(11): p. 1536-40.

Figure 1.

A


Treatment Duration
1.0
0.8
0.6
0.4
0.2
0.0
0
200
400
600
80
Days
Good: RMH Score: 0-1
Poor: RMH Score: 2-3

B

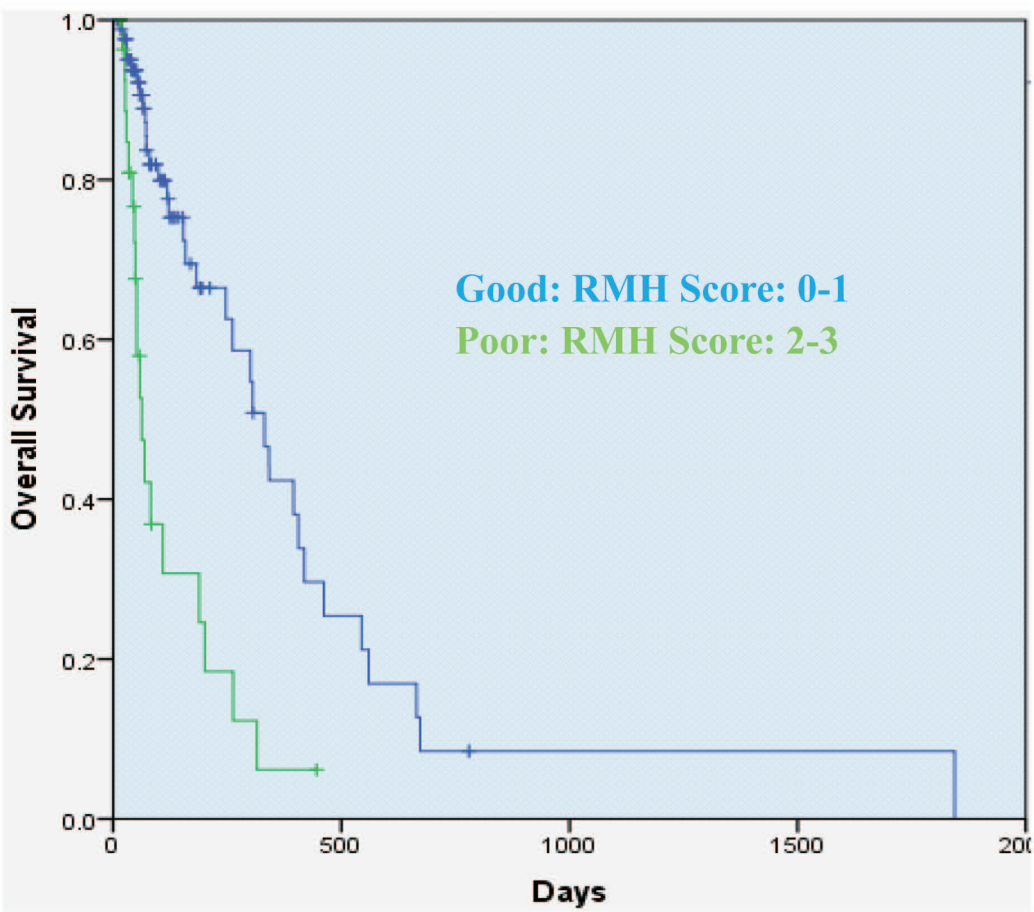

Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
500
1000
1500
200
Days
Good: RMH Score: 0-1
Poor: RMH Score: 2-3

Table 1. Patient characteristics (*N*=115)

Characteristics	
Age (median (range))	59 (30, 85)
Male/Female	84/31
Caucasian/Asian/African/Others/Unknown	89/5/4/3/14
Esophagus/EGJ/Stomach	54/14/47
Histology (Adeno/Squamous/Not known)	103/10/2
ECOG PS (0/1/2)	26/84/5
Prior Surgery N(%)	42 (37)
Prior Radiation N(%)	31 (27)
No. of Metastatic Sites (median (range))	2 (0, 6)
No. of Metastatic Sites (≤2/>2)	85/30
Hemoglobin (g/dl) (median (range))	11.9 (9.0, 16.0)
LDH (median (range))	183 (91, 3156)
Platelet Count ($x10^3/\mu L$) (median (range))	260 (104, 797)
Albumin (g/dl) (median (range))	3.6 (2.1, 4.6)
Royal Marsden Hospital (RMH) Score (0/1/2/3)	40/46/25/4
No. of Previous Treatments (0-2/3-4/>4)	44/20/51

Table 2. Type of Phase 1 Study (*N*=115)

Type of Phase 1 Study	**Number of Patients *N* (%)**
Monotherapy (17 studies)	32 (28%)
Chemotherapy only (3 studies)	8 (7%)
Biologic only (14 studies)	24 (21%)
Combination therapy (27 studies)	83 (72%)
Chemotherapy combination (0 study)	0 (0%)
Biologic combination (10 studies)	18 (16%)
Biologic + Chemotherapy (17 studies)	65 (56%)
Total (44 studies)	115 (100%)

Table 3. Safety profiles

	good RMH † **Score (0-1)** ***(N=86)***	**poor RMH** † **Score (2-3)** ***(N=29)***	**Total** ***(N=115)***
Dose limiting toxicity (DLT)	14 (16%)	7 (24%)	21 (18%)
General disorder	4 (5%)	1 (3%)	5 (4%)
Gastrointestinal disorder	3 (4%)	2 (7%)	5 (4%)
Blood system disorder	6 (7%)	4 (14%)	10 (9%)
Cardiac disorder	1 (1%)	0 (0%)	1 (1%)
Toxic events of grade 3 or 4	62 (72%)	25 (86%)	87 (76%)
Toxic events of grade 5 (Treatment Related Death)	0 (0%)	1 (3%)	1 (1%)

† Royal Marsden Hospital

Table 4. Treatment Responses (*N*=115)

Best response	**good RMH** [†] **Score (0-1)** ***(N=86)***	**poor RMH** [†] **Score (2-3)** ***(N=29)***	**Total** ***(N=115)***
Complete Response (CR)	0 (0%)	0 (0%)	0 (0%)
Partial Response (PR)	7 (8%)	1 (3%)	8 (7%)
Stable Disease (SD)	35 (41%)	4 (14%)	39 (34%)
Progressive Disease (PD)	30 (35%)	22 (76%)	52 (45%)
Not Evaluated (NE)	14 (16%)	2 (7%)	16 (14%)
Total	86 (100%)	29 (100%)	115 (100%)
Response Rate (CR+PR)	8%	3%	7%
Disease control rate (CR+PR+SD)	49%	17%	41%

[†] Royal Marsden Hospital

Table 5. Univariate and Multivariate Analysis of Overall survival by Patient Characteristics (*N*=115)

	Univariate	**Multivariate**[†]		
Characteristics	***P* value**	**Hazard Ratio**	**95% CI**	***P* value**
Age				
<60 (*N*=58)	0.064	0.562	0.320-0.990	0.046
≥60 (*N*=57)				
Male/Female				
Female (*N*=31)	0.475			
Male (*N*=84)				
Esophagus/esophago-gastric junction (EGJ), Stomach				
Esophagus, EGJ (*N*=68)	0.198			
Stomach (*N*=47)				
ECOG Performance Status				
0 or 1 (*N*=110)	<0.001	0.214	0.059-0.778	0.019
2 (*N*=5)				
Hemoglobin (g/dl)				

<10 (*N*=12)	0.127			
≥10 (*N*=103)				
Platelet Count (x10^3/μL)				
<150 (*N*=12)	0.76			
≥150 (*N*=103)				
LDH				
≤ULN†† (*N*=73)	<0.001			
>ULN†† (*N*=42)				
Albumin (g/dl)				
≥3.5 (*N*=79)	<0.001			
<3.5 (*N*=36)				
Number of Sites of Metastasis				
0-2 (*N*=85)	0.111			
>2 (*N*=30)				
Royal Marsden Hospital (RMH) Prognosis				
0 or 1 (*N*=86)	<0.001	0.294	0.159-0.545	<0.001
2 or 3 (*N*=29)				

No. of Previous Treatments				
≤3 (*N*=56)	0.128			
>3 (*N*=59)				

[†]Multivariate analysis with RMH Score but not including its components (LDH level, albumin level, and number of metastatic sites of disease).

[††]ULN: Institutional upper limit of normal