# Post progression survival analysis of metastatic gastric and gastroesophageal junction cancer patients after second-line treatment

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## Abstract

***Purpose :*** **The aim of this study was to define the factors that affect response and post-progression survival of metastatic gastric cancer (MGC) and gastroesophageal junction cancer (GEJ) patients treated with second-line chemotherapy.**

***Methods :*** **We retrospectively reviewed the data of 59 patients with MGC or GEJ adenocarcinoma who received second-line treatment.**

***Results :*** **The median age was 54 years old (26-77). Response to second-line treatment was strongly associated with disease control with first-line treatment ($p < 0.01$). Median progression-free survival (PFS), overall survival (OS) and post-progression survival (PPS) were 3.2 (95% CI : 2.63-3.80), 6.5 (95% CI : 3.78-9.35) and 2.7 months (95% CI : 1.89-3.68), respectively. PFS ($r = 0.55$, $p < 0.01$) and PPS ($r = 0.89$, $p < 0.01$) were correlated with OS. Response to second-line treatment was independently related to PFS (HR : 0.12 95%CI : 0.53-0.26, $p < 0.001$). Having an ECOG 0 performance status (HR : 0.42 ; 95%CI : 0.21-0.86, $p = 0.02$) and response to second-line therapy (HR : 0.47 ; 95%CI : 0.25-0.85, $p = 0.01$) were independently associated with OS.**

***Conclusion :*** **PPS and PFS were correlated with OS after second-line treatment of MGC. Response to second-line treatment prolonged OS by increasing PFS, and having an ECOG 0 PS prolonged OS by increasing PPS.** (Acta gastroenterol. belg., **2016**, 79, **211-215**).

**Key words** : metastatic gastric cancer, post progression survival, overall survival performance status, second-line treatment, post progression survival.

## Introduction

Gastric cancer is one of the most lethal malignancies. In 2015, an estimated 24,590 new gastric cancer cases will be diagnosed, and 10,720 people will die of gastric cancer in the United States (1). For local and locoregional disease, surgery followed by adjuvant chemotherapy or chemoradiation or perioperative chemotherapy is the standard treatment modality (2). Approximately 40% of the patients are diagnosed at the metastatic stage, and a significant proportion of the patients progress to the metastatic stage (3). The five-year survival rate is less than 5% for metastatic gastric cancer (MGC) (4). The only treatment option for MGC is palliative chemotherapy. Palliative chemotherapy can improve survival compared to BSC, and combination chemotherapies provide longer survival than single-agent 5-FU (5). The median survival with first-line standard chemotherapy is less than 1 year.

After first-line therapy, some patients, especially those who have good general conditions, are candidates for second-line therapy. Some of the factors that predict the efficacy of the second-line treatment have been defined. A recently published meta-analysis showed that second-line chemotherapy provided a survival advantage (6). In first-line treatment, progression free survival (PFS) and post progression survival (PPS) are correlated with overall survival (OS) (7). Therefore, any factor that affects PPS can also affect OS. To the best of our knowledge, there have been no published data in the literature in English about PPS after second-line treatment of MGC. In this retrospective study, we reported our experience with second-line therapy for metastatic gastric adenocarcinoma. We aimed to define the factors that affected response and PPS.

## Methodology

We retrospectively evaluated the medical records of patients with recurrent gastric carcinoma, including gastroesophageal junction cancer (GEJ), who were treated at Trakya University Medical Oncology Clinic between January 2007 and July 2014. A total of 59 patients were started on second-line therapy after palliative front-line therapy. Patients older than 18 years of age with histologically proven advanced gastric adenocarcinoma were included in the study. The study was approved by the ethics committee of our institution.

The demographic and clinical information of the patients were obtained from the patients' records. Response evaluations were performed every 8-10 weeks according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. Clinical deterioration and death due to disease before radiologic examination were also accepted as disease progression. Disease control with first-line treatment was defined as stable disease or partial or complete response according to RECIST for advanced disease at more than 6 months after the initiation of chemotherapy. The response rate (RR) was defined as the proportion of stable disease or partial or complete response according to RECIST for advanced disease in all

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Submission date : 07/08/2015
Acceptance date : 22/01/2016

of the patients. Factors related to disease control and response rate were analysed using Pearson's $\chi^2$test or Fisher's exact test.

Progression-free survival was calculated from the start of second-line chemotherapy to the date of radiologic or clinical disease progression. Overall survival was calculated from the start of second-line chemotherapy to the date of death from disease or the last follow-up. Post-progression survival was calculated from the date of disease progression after second-line chemotherapy to the date of death from disease or the last follow-up. Survival estimates were calculated using the Kaplan-Meier method. The log-rank test was used to assess the disease- and treatment-related prognostic factors. Correlation coefficients (r) and their significance in survival were calculated using Pearson's test. For multivariate analysis of prognostic factors, the Cox proportional hazards regression model was used. The prognostic factors were age, sex, location of the tumour, stage at diagnosis, Eastern Cooperative Oncology Group Performance Status (ECOG PS) before second-line therapy, number of metastatic sites before second-line therapy, the presence of peritoneal metastasis, disease control with first-line therapy and chemotherapy. A $p$ value < 0.05 was considered statistically significant.

## Results

Fifty-nine patients started second-line treatment between January 2007 and July 2014 at our clinic. The median age was 54 years old (range, 26 to 77 years), and 43 patients (62.9%) were male. Fifty-one patients (86.4%) had died by the time of the analysis ; all of the deaths were due to disease progression. The primary tumour site was the stomach in 49 patients (83.1%) and the GEJ in 10patients (16.9%). Eighteen of the patients underwent curative surgical treatment and all of them received adjuvant chemoradiation. Forty-one patients were metastatic at the time of the diagnosis (Table 1). All of the patients received platinum- and fluoropyrimidine-containing combination chemotherapies for the first-line treatment of metastatic disease (Table 2). The liver (58.1%) and peritoneum (31.7%) were the two most common recurrence sites before second-line therapy. As second-line therapy, 50 patients (84.7%) received combination chemotherapy, and 9 patients (15.3%) received single-agent chemotherapy. Fluoropyrimidine-irinotecan combination (FOLFIRI) was the most commonly preferred combination therapy (Table 2).Thirteen patients (22.0%) received third-line chemotherapy. The most frequently administered third-line treatment was fluoropyrimidine-oxaliplatin combination (five patients, 38.4%).

The response rate to second-line therapy was 37.7% (10 partial responses, 12cases of stable disease). Age, sex, tumour location, stage at diagnosis, ECOG performance status, site of metastasis and combination chemotherapy were not related to response to second-line treatment (Table 3). Disease control with first-line therapy was significantly associated with response to second-line treatment (p < 0.01). In 17 of the 20 (85.0%) patients in whom disease control could not be achieved with first-line treatment, disease response to second-line treatment was not achieved. In multivariate analysis, disease control with first-line treatment was an independent predictor of response to second-line treatment (HR : 0.22 ; 95%CI : 0.05-0.93, p = 0.04). The RR after third-line treatment was 30.7% (4 SD). All of the patients with stable disease after third-line treatment had disease control with first-line treatment.

The median estimated PFS, OS and PPS were 3.2 months (95% CI : 2.63-3.80), 6.5 months (95%CI : 3.78-9.35) and 2.7 months (95% CI ; 1.89-3.68), respectively. Both PFS (r = 0.55, p < 0.01) and PPS (r = 0.89, p < 0.01) were correlated with OS. Disease control with first-line therapy tended to increase PFS (p = 0.05). Progression-free survival, PPS and OS were not correlated with age, sex, stage at initial diagnosis, location of tumour, number of metastatic sites, peritoneal metastasis or receiving combination chemotherapy (Table 4). In patients whose disease responded to second-line therapy, PFS (7.3 months vs. 2.7 months ; p < 0.01) and OS (10.2 months vs. 5.2 months ; p < 0.01) were significantly longer. Patients with good performance scores had

Table 1. — **Demographic and clinical characteristics of patients**

| | n (percent) |
|---|---|
| Overall | 59 (100%) |
| Sex | |
| Male | 43 (72.9%) |
| Female | 16 (27.1%) |
| Median Age | 54 (26-77) |
| ≥ 60 | 11 (22.0%) |
| < 60 | 46 (78.0%) |
| Location of tumour | |
| Gastroesophageal junction | 10 (16.9%) |
| Corpus | 35 (59.4%) |
| Antrum | 14 (23.7%) |
| Stage at diagnosis | |
| Early | 21 (35.6%) |
| Metastatic | 38 (64.4%) |
| Disease control at first-line therapy | |
| Yes | 29 (69%) |
| No | 12 (29%) |
| PS before second-line therapy | |
| Good (ECOG 0) | 17 (28.8%) |
| Poor (ECOG 1-2) | 42 (71.2%) |
| Number of metastatic sites | |
| One site | 22 (37.3%) |
| Multiple | 37 (62.7%) |
| Peritoneal metastasis | |
| Yes | 28 (47.5%) |
| No | 31 (52.5%) |
| Second-line therapy | |
| Combination | 50 (84.7%) |
| Single agent | 9 (15.3%) |

Table 2. — **Chemotherapy regimens**

| | First-line | Second-line |
|---|---|---|
| Combination | | 50 (84.7%) |
| DCF | 38 (64.4%) | 7 (11.9%) |
| FOLFIRI | – | 34 (57.5%) |
| mFOLFOX6 | 11 (18.6%) | 6 (10.2%) |
| CP | 6 (10.2%) | 3 (5.1%) |
| PEF | 4 (6.8%) | – |
| Single Agent | | 9 (15.3%) |
| Irinotecan | | 3 (5.1%) |
| Capecitabine | | 2 (3.4%) |
| Docetaxel | | 4 (6.8%) |

DCF : docetaxel 75 mg/m$^2$ (day 1), 5-FU 750 mg/m$^2$ (46 hinfusion), cisplatin 75 mg/m$^2$ (day 1) q21d. FOLFIRI : irinotecan 180 mg/m$^2$ (day 1), folinic acid 400 mg/m$^2$ (day 1), 5-FU 400 mg/m$^2$ (day 1), 5-FU 2400 mg/m$^2$ (46 h infusion) q14d. mFOLFOX6 : oxaliplatin 85 mg/m$^2$ (day 1), folinic acid 400 mg/m$^2$ (day 1), 5-FU 400 mg/m$^2$ (day 1), 5-FU 2400 mg/m$^2$ (46 h infusion) q14d. CP : cisplatin 75 mg/m$^2$ (day 1) q21d, PEF : cisplatin 60 mg/m2 (day 1), 5-FU 600 mg/m$^2$ (day 1), epirubicin 60 mg/m2 (day 1) q21d.

Table 3. — **Factors related to responseto second-line chemotherapy (n %)**

| | N (percent) | p |
|---|---|---|
| Overall | 22 (100%) | |
| Sex | | 0.23 |
| Male | 18 (81.8%) | |
| Female | 4 (18.2%) | |
| Age | | 0.58 |
| ≥ 60 | 4 (18.2%) | |
| < 60 | 18 (81.8%) | |
| Location of tumour | | 0.65 |
| Gastroesophageal junction | 5 (22.7%) | |
| Corpus | 12 (54.5%) | |
| Antrum | 5 (22.7%) | |
| Stage at diagnosis | | 0.64 |
| Early | 7 (31.8%) | |
| Metastatic | 15 (68.2%) | |
| Disease control at first-line therapy | | 0.01 |
| Yes | 19 (86.4%) | |
| No | 3 (13.6%) | |
| PS before second-line therapy | | 0.11 |
| Good (ECOG 0) | 9 (40.9%) | |
| Poor (ECOG 1-2) | 13 (59.1%) | |
| Number of metastatic sites | | 0.22 |
| One site | 8 (44.4%) | |
| Multiple | 10 (55.6%) | |
| Peritoneal Metastasis | | 0.76 |
| Yes | 11 (50.0%) | |
| No | 11 (50.0%) | |
| Second-line therapy | | 0.13 |
| Combination | 1 (4.5%) | |
| Single agent | 21 (95.5%) | |

significantly longer OS (8.6 months vs. 5.9 months, p = 0.01) and PPS (3.6 months vs. 2.1 months, p = 0.01) ; however, performance status was not correlated with PFS (4.6 months vs. 3.0 months, p = 0.33) (Table 4) (Fig. 1). In multivariate analysis, response to second-line treatment was the only independently correlated with PFS (HR : 0.12 95%CI : 0.53-0.26, p < 0.001), while having an ECOG 0 performance score (HR : 0.42 ; 95%CI : 0.21-0.86, p = 0.02) and response to second-line therapy (HR : 0.47 ; 95%CI : 0.25-0.85, p = 0.01) were independently associated with OS. Moreover, having an ECOG 0 performance was also independently associated with PPS (HR : 0.42 ; 95%CI : 0.20-0.93, p = 0.03) in multivariate analysis. Response to second-line treatment prolonged OS by increasing PFS, and having an ECOG 0 PS prolonged OS by increasing PPS. The PPS of 11 patients (18.6%) was longer than 6 months. In five of these patients (45.4%, 2 PR, 3 SD), disease response was obtained with second-line therapy. Eight of them received third-line therapy, and in 3 patients, disease response was obtained.

## Discussion

Even if disease response is achieved with first-line therapy, all patients with MGC subsequently experience disease progression. Patients who have a good general condition after front-line therapy are candidates for further treatment. In several randomized, prospective studies, second-line chemotherapy has been compared with best supportive care (BSC). In these studies, second-line treatment provided an OS advantage with single-agent irinotecan and docetaxel (8-10). A meta-analysis of these trials proved the efficacy of second-line treatment for OS in pretreated advanced gastric cancer (11). Several combination regimens have also been reported as effective second-line treatments (12, 13). Furthermore, new agents targeting vascular endothelial growth factor receptor, including ramucirumab and apatinib, have been effective insalvage therapy for advanced gastric cancer patients (14, 15). The primary end point of these studies was OS. Shitara *et al*. (7) reported that PFS and PPS were correlated with OS in first-line treatment of advanced gastric cancer. In other words, PFS and PPS both determined OS. Until now, PPS and factors related to it after second-line treatment of MGC patients had not been reported.

The most important issue is determining which patients will benefit from second-line treatment. Kanagavel *et al*. (16) developed a prognostic model that included ECOG PS, haemoglobin level and time to progression under first-line therapy. They concluded that, in patients with good ECOG PS (0-1), higher haemoglobin levels (≥ 10 g/dl) and longer time to progression (≥ 5 months), second-line chemotherapy was effective. In another study, ECOG PS of 2,a serum albumin level less than 3.5 g/dl and time to progression shorter than 170 days on first-line therapy were found to be negative prognostic factors. Authors have suggested that patients who have two or more of these negative prognostic factors would not benefit from second-line chemotherapy (17). Low serum albumin level, poor performance status, poor histologic type, and short PFS on second-line treatment

Table 4. — **Factors related to progression-free survival, post-progression survival and overall survival**

| | PFS (months) (95% CI) | p | OS (months) (95% CI) | p | PPS (months) (95% CI) | p |
|---|---|---|---|---|---|---|
| Sex | | | | | | |
| Male | 3.2 (2.36-4.07) | 0.31 | 8.7 (6.60-10.91) | 0.81 | 2.7 (1.61-3.96) | 0.74 |
| Female | 3.1 (2.22-4.15) | | 8.4 (5.56-11.35) | | 2.6 (0.05-5.26) | |
| Age | | | | | | |
| ≥ 60 | 2.8 (1.95-3.69) | 0.91 | 6.3 (0.56-13.49) | 0.45 | 2.0 (0.61-3.39) | 0.53 |
| < 60 | 3.4 (2.81-4.08) | | 7.6 (4.71-10.59) | | 2.9 (2.14-3.76) | |
| Location of tumour | | | | | | |
| GEJ | 3.6 (0.91-6.31) | 0.97 | 8.6 (7.55-9.79) | 0.53 | 3.3 (2.31-4.45) | 0.52 |
| Corpus | 3.0 (2.56-3.47) | | 6.0 (4.36-7.72) | | 2.59 (1.75-3.44) | |
| Antrum | 3.5 (2.38-4.64) | | 8.2 (2.39-14.10) | | 3.0 (0.12-6.10) | |
| Stage at diagnosis | | | | | | |
| Early | 2.8 (1.53-4.18) | 0.29 | 8.4 (5.54-11.27) | 0.88 | 3.3 (0.13-6.56) | 0.99 |
| Metastatic | 3.5 (2.73-4.16) | | 6.3 (2.97-9.63) | | 2.6 (2.10-3.22) | |
| Disease control at first-line | | | | | | |
| Yes | 3.5 (2.93-4.10) | 0.05 | 8.6 (8.01-9.20) | 0.03 | 2.7 (2.28-3.30) | 0.22 |
| No | 2.3 (1.56-3.10) | | 5.5 (3.15-7.94 | | 2.1 (0.68-3.65) | |
| Performance | | | | | | |
| Good (ECOG 0) | 4.6 (1.70-7.68) | 0.33 | 8.6 (4.23-12.97) | 0.01 | 3.6 (2.75-4.54) | 0.01 |
| Poor (ECOG 1-2) | 3.0 (2.36-3.68) | | 5.9 (0.87-4.20) | | 2.1 (0.80-3.52) | |
| Number of metastatic sites | | | | | | |
| One site | 3.4 (2.53-4.42) | 0.46 | 8.2 (2.84-13.65) | 0.91 | 3.0 (2.23-3.87) | 0.45 |
| Multiple | 3.2 (2.62-3.75) | | 7.6 (4.57-10.73) | | 1.4 (0.38-2.43) | |
| Peritoneal metastasis | | | | | | |
| Yes | 3.1 (2.28-4.09) | 0.52 | 6.5 (3.57-9.57) | 0.31 | 2.9 (2.22-3.69) | 0.48 |
| No | 3.2 (2.50-3.93) | | 8.2 (4.83-11.65) | | 2.8 (1.89-3.68) | |
| Second-line therapy | | | | | | |
| Combination | 3.4 (2.96-4.00) | 0.27 | 8.2 (5.51-10.97) | 0.70 | 3.0 (2.31-3.79) | 0.61 |
| Single agent | 2.8 (2.14-3.50) | | 4.1 (3.21-5.13) | | 2.0 (0.66-3.34) | |
| Response to Second-line therapy | | | | | | |
| Yes | 7.3 (6.20-8.51) | < 0.01 | 10.2 (8.62-11.93) | < 0.01 | 3.4 (2.25-4.57) | 0.25 |
| No | 2.6 (2.17-3.15) | | 5.2 (4.20-6.24) | | 2.0 (0.56-3.50) | |

GEJ, Gastroesophageal junction.

were poor prognostic factors for third-line chemotherapy (18). Good performance status and longer time to progression on first-line treatment were the most important prognostic factors. Anaemia and albumin levels were indirectly correlated with performance status. In the current study, as in previous studies, disease control with first-line treatment was a predictor of response to second-line treatment and an ECOG PS of 0 was a good prognostic factor.

Overall survival was correlated with PFS and PPS. In the current analysis, we found that, although having an ECOG PS of 0 was correlated with OS and PPS, it was not related to response rate or PFS. In general, patients with poor performance status have comorbid diseases, high tumour burdens or disease-related complications. Therefore, although they were treated with second-line chemotherapy, they probably had short OS because of poor PPS. Response to second-line treatment had no impact on PPS ; however, it prolonged OS by prolonging PFS.

Nearly one-third of the patients who were able to receive third-line chemotherapy remained chemo-sensitive despite two previous lines of therapy. Moreover, one-fifth of the patients after progression on second-line treatment lived longer than 6 months. There might be a subgroup of patients with good prognosis, as in breast cancer. Four genomic subtypes of gastric adenocarcinoma have been defined by molecular analysis. These four subtypes, including Epstein-Barr virus-infected tumours, microsatellite unstable tumours, genomically stable tumours and chromosomally unstable tumours, have different genomic properties and mutations (19). This biologic diversity inevitably affects the clinical features of the gastric cancer. Although the prognostic importance of some of the biologic markers has been studied in gastric cancer, these markers have not yet been integrated into daily clinical practice, except for human epidermal growth factor receptor 2 overexpression (20-22).

The retrospective nature of this study was the main limitation. We did not analyse any biologic markers. Another important issue in second-line treatment of incurable diseases is the improvement or sustaining of quality of life. However, due to the retrospective nature of the study, we could not evaluate it. In this analysis, we also

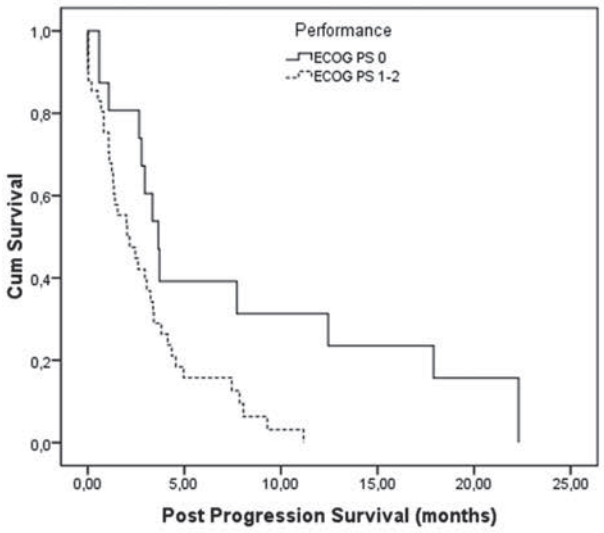


Fig. 1

focused on the PPS of the patients. Because PFS and PPS together determine OS, any factor that affects PPS can change OS. We demonstrated that asymptomatic patients with MGC had longer OS because of longer PPS.

In conclusion, PPS and PFS were correlated with OS after second-line treatment of metastatic gastric and gastroesophageal junction cancer. Response to second-line treatment prolonged OS by increasing PFS, and having an ECOG 0 PS prolonged OS by increasing PPS. Asymptomatic patients had longer PPS and OS. Performance status might not be a good factor for deciding on second-line treatment because patients with poor performance status despite similar RR and PFS to patients with good performance status have poor OS due to having short PPS. Second-line treatment for metastatic gastric cancer that progresses after front-line chemotherapy should be considered in patients whose disease could have been controlled with first-line treatment. New prospective studies that incorporate tumour biology are needed.

## References


1. SIEGEL R.L., MILLER K.D., JEMAL A. Cancer statistics, 2015. *CA : a cancer journal for clinicians*, 2015, **65** (1) : 5-29.
2. WADDELL T., VERHEIJ M., ALLUM W., CUNNINGHAM D., CERVANTES A., ARNOLD D. Gastric cancer : ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*, 2013, **24** Suppl 6 : vi57-63.
3. SIEGEL R., MA J., ZOU Z., JEMAL A. Cancer statistics, 2014. *CA : a cancer journal for clinicians*, 2014, 64 (1) : 9-29.
4. CHANG Y.R., HAN D.S., KONG S.H. *et al*. The value of palliative gastrectomy in gastric cancer with distant metastasis. *Annals of surgical oncology*, 2012, **19** (4) : 1231-1239.
5. WAGNER A.D., UNVERZAGT S., GROTHE W. *et al*. Chemotherapy for advanced gastric cancer. *The Cochrane database of systematic reviews*, 2010 (3) : Cd004064.
6. IACOVELLI R., PIETRANTONIO F., FARCOMENI A. *et al*. Chemotherapy or targeted therapy as second-line treatment of advanced gastric cancer. A systematic review and meta-analysis of published studies. *PloS one*, 2014, **9** (9) : e108940.
7. SHITARA K., MATSUO K., MURO K., DOI T., OHTSU A. Progression-free survival and post-progression survival in patients with advanced gastric cancer treated with first-line chemotherapy. *Journal of cancer research and clinical oncology*, 2013, **139** (8) : 1383-1389.
8. THUSS-PATIENCE P.C., KRETZSCHMAR A., BICHEV D. *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). *European journal of cancer (Oxford, England : 1990)*, 2011, **47** (15) : 2306-2314.
9. KANG J.H., LEE S.I., LIM DO 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. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 2012, **30** (13) : 1513-1518.
10. FORD H.E., MARSHALL A., BRIDGEWATER J.A. *et al*. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02) : an open-label, phase 3 randomised controlled trial. *The Lancet Oncology*, 2014, **15** (1) : 78-86.
11. KIM H.S., KIM H.J., KIM S.Y. *et al*. Second-line chemotherapy versus supportive cancer treatment in advanced gastric cancer : a meta-analysis. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*, 2013, **24** (11) : 2850-2854.
12. RINO Y., YUKAWA N., SATO T. *et al*. Phase II study on the combination of irinotecan plus cisplatin as a second-line therapy in patients with advanced or recurrent gastric cancer. *Molecular and clinical oncology*, 2013, **1** (4) : 749-752.
13. LIN R., FAN N., WU G. *et al*. A phase 2 study of fluorouracil/leucovorin in combination with paclitaxel and oxaliplatin as a salvage treatment in patients with refractory or relapsed advanced gastric cancer. *Journal of chemotherapy (Florence, Italy)*, 2015, **27** (1) : 52-56.
14. LI J., QIN S., XU J. *et al*. Apatinib for chemotherapy-refractory advanced metastatic gastric cancer : results from a randomized, placebo-controlled, parallel-arm, phase II trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 2013, **31** (26) : 3219-3225.
15. FUCHS C.S., TOMASEK J., YONG C.J. *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) : 31-39.
16. KANAGAVEL D., POKATAEV I.A., FEDYANIN M.Y. *et al*. A prognostic model in patients treated for metastatic gastric cancer with second-line chemotherapy. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*, 2010, **21** (9) : 1779-1785.
17. HASEGAWA H., FUJITANI K., NAKAZURU S., HIRAO M., MITA E., TSUJINAKA T. Optimal indications for second-line chemotherapy in advanced gastric cancer. *Anti-cancer drugs*, 2012, **23** (4) : 465-470.
18. SHIM H.J., YUN J.Y., HWANG J.E., BAE W.K., CHO S.H., CHUNG I.J. Prognostic factor analysis of third-line chemotherapy in patients with advanced gastric cancer. *Gastric cancer : official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association*, 2011, **14** (3) : 249-256.
19. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*, 2014, **513** (7517) : 202-209.
20. GUO J., XIAO J.J., ZHANG X., FAN K.X. CD40 expression and its prognostic significance in human gastric carcinoma. *Medical oncology (Northwood, London, England)*, 2015, **32** (3) : 463.
21. FUSE N., KUBOKI Y., KUWATA T. *et al*. Prognostic impact of HER2, EGFR, and c-MET status on overall survival of advanced gastric cancer patients. *Gastric cancer : official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association*, 2015.
22. BANG Y.J., VAN CUTSEM E., FEYEREISLOVA A. *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) : 687-697.