frequent pattern of recurrence was intrahepatic recurrence, observed in 79 % (166 of 209) of all the recurrences reported.

Mortality was 1.1 % (5/426) among the 15 studies in which the data were available, and morbidity ranged from 19 % to 47 % among 6 studies.

The 5-year survival reported from each series ranged from 0 % to 37 % and exceeded 30 % in five series [6, 10, 12, 15, 16]. Median survival time ranged from 9 to 38.8 months. The diversity in outcome may have reflected the diversity in patient selection and strategy taken, including the use of adjuvant therapies. The 5-year survival of all patients analyzed in the current study, calculated by dividing the number of 5-year survivors reported in each article by the total number of patients, was 18.8 % (97 of / 515). Although these series should be considered to represent a well-selected and more favorable population compared with patients with liver metastases who were treated with systemic chemotherapy and had poorer outcome, the 5-year survival rate at 18.8 % obtained cannot be ignored as futile. Gastric cancer with liver metastases has long been considered as a systemic disease with no indication for surgery with curative intent. This point has been made clear, both in the National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2013 [23] and in the Japanese Guidelines [5]. However, there are occasions when such metastases are found as clinically resectable disease, and whether these exceptions should still be treated either by palliative chemotherapy or supportive care could be an issue for debate.

Indication for surgery has not been established but could be considered based on analysis of prognostic factors. Independent prognostic factors identified through multivariate analyses were varied, and included the number of metastatic nodules, unilobular distribution, solitary tumor, tumor diameter, and capsular formation regarding hepatic tumors (Table 2). Among these, the "number of metastatic nodules" was considered to be an important factor across several series if "solitary metastasis" was to be included. Among 319 patients with relevant information in the current series, 195 (61.1 %) actually had solitary metastases. One should note, however, that the number of nodules can differ, depending on the type of imaging studies used [24, 25]. Because most institutions needed more than a decade to accumulate 15 patients or more, there should have been much difference in the potential of imaging modalities at the beginning and the end of the study period. In the largest single-institution series, Takemura et al.[6] reported a 5-year survival of 37 %. It may be of note that they currently consider surgery when the number of metastatic nodules was diagnosed as three or fewer, using state-of-the-art imaging tools. As for other prognostic factors, some have found metachronous hepatic metastases to be a sign of favorable prognosis [11, 12, 20] whereas others consider this as irrelevant. In addition, status of the primary tumor such as serosal invasion, lymphatic invasion, and clinical stage were listed as relevant prognostic factors.

It may be worthwhile to mention that the incidence of clinically resectable hepatic metastasis may be lower than what a surgeon expects. Sakamoto et al. [14] reported that they found synchronous liver metastases in 2.2 % of the 5,209 patients who underwent gastrectomy at National Cancer Center, Japan, whereas 1.3 % developed metachronous metastases. About 20 % of these patients underwent hepatectomy for cure. In contrast, 1,013 of 10,259 patients (9.9 %) diagnosed as gastric cancer in the Yonsei University Health System, Korea, had synchronous or metachronous liver metastases [9]. Of these, 58 had metastases confined to the liver and 41 (only 4 % of all patients with liver metastases) underwent surgery with curative intent, which denotes management of both the primary tumor and the liver. The five-year survival rate of these 41 patients was 20.8 %, and the median survival time fell just short of 20 months. In short, 20 % of the patients with liver metastases can be treated surgically in a situation where only patients with potentially resectable disease are referred, a situation possibly encountered at the surgical department in a high-volume cancer center. In contrast, resectable liver metastasis undoubtedly is a rare disease when one attempts to carefully select patients from all gastric cancer patients who visit a hospital.

Indication for the adjuvant therapy given perioperatively was even more varied among the researchers, as no trial-based evidence exists for the population who underwent hepatectomy for gastric cancer metastasis. Takemura et al. [6] took an aggressive approach in which 18 of 73 patients received neoadjuvant chemotherapy and 31 received postoperative chemotherapy, including 5 cases that received arterial infusion (HAIC) postoperatively. In contrast, Sakamoto et al. [14] reported that they delivered chemotherapy only for those who subsequently had recurrences. There is no prospective trial showing the effect of perioperative adjuvant therapies for gastric cancer metastases to the liver. The high incidence of recurrence implies that micrometastases remain in situ after surgery, however. That micrometastases could be managed by modern chemotherapeutic agents has been proven by several adjuvant chemotherapy trials [26–28]. Thus, there is a rationale for perioperative chemotherapy, or even HAIC, given the high incidence of recurrence within the liver. Chemotherapy delivered preoperatively could be useful to identify cancers that do not respond to chemotherapy and progress rapidly and to avoid futile surgery. All five series with 5-year survival >30 % reported details on adjuvant strategies, including neoadjuvant chemotherapy and HAIC. In contrast, none of the patients received chemotherapy until

Table 2 Independent prognostic determinants of the patients with gastric cancer liver metastasis

	Indication for inclusion in the case series	Factors independently showing favorable prognosis
Takemura et al. [6]	All hepatectomy cases	No serosal invasion, diameter <5 cm
Wang et al. [8]	Hepatectomy cases of synchronous metastasis	Solitary liver tumor, absence of peritoneal metastasis
Schildberg et al. [20]	All hepatectomy cases	Solitary liver tumor, synchronous metastasis
Garancini et al. [19]	All hepatectomy cases	Solitary liver tumor, RO resection, capsule formation
Miki et al. [8]	All cases with hepatic metastasis	Stage of the primary cancer
Makino et al. [10]	All cases with hepatic metastasis who underwent gastrectomy	Unilobular distribution
Tsujimoto et al. [17]	All hepatectomy cases	Diameter <6 cm, D2 dissection
Cheon et al. [9]	All cases with hepatic metastasis who underwent laparotomy with curative intent	Smaller number of metastases
Thelen et al. [16]	All hepatectomy cases	Negative resection margin
Morise et al. [15]	All hepatectomy cases	
Sakamoto et al. [14]	All hepatectomy cases	Unilobular distribution, diameter <4 cm
Adam et al. [2]	All hepatectomy cases of noncolorectal nonneuroendocrine hepatic metastasis	
Shirabe et al. [7]	All hepatectomy cases who underwent RO resection	Number of metastases <3, no lymphatic or venous invasion of the primary tumor
Zacherl et al. [13]	All hepatectomy cases	
Okano et al. [12]	All hepatectomy cases	Solitary liver tumor, synchronous metastasis, well-differentiated phenotype, capsule formation
Ambiru et al. [11]	All hepatectomy cases	Synchronous metastasis
Imamura et al. [21]	All hepatectomy cases of gastric and colorectal liver metastasis	No extrahepatic metastasis

recurrence in another series by Sakamoto et al., who reported their 5-year survival at 11 % as unsatisfactory. These facts imply the relevance of perioperative chemotherapy, although outcomes obtained from retrospective case series should be interpreted with caution. Evidence at a higher level will not be available for the time being because the chances of conducting a decently designed trial to generate evidence for adjuvant therapies in a disease as rare as resectable gastric liver metastases would be sparse.

Systemic chemotherapy, HAIC, and radiofrequency ablation (RFA) are among other treatment modalities for gastric cancer metastasis to the liver. No prospective trial investigating systemic chemotherapy specified in hepatic metastases has been reported, with the exception of one small pilot study involving 8 patients [29]. In recent phase III trials of first-line chemotherapy against advanced/metastatic gastric cancer, median survival time ranged from 11 to 15 months [30–34]; 5-year survivors were rarely observed. In a report that integrated 643 patients enrolled in five separate prospective trials performed by the Japan Clinical Oncology Group, the 5-year survival rate of patients with metastasis confined to the liver and treated with systemic chemotherapy alone was 1.7 % [35]. Presumably, this series does not include patients with a relatively small cancer burden for whom indication for surgery was seriously considered, and comparison of survival data with those of highly selected patients who underwent surgical resection of the metastases needs to be interpreted with caution. Nevertheless, it remains impractical to hope to cure patients with gastric cancer metastases to the liver by systemic chemotherapy.

The rationale for HAIC is in high intrahepatic drug concentration in relationship to the systemic concentration [36]. A response rate >50 % has been reported that led to good local control [36, 37]. However, good local control did not necessarily lead to prolonged survival in cases of gastric cancer, in which extrahepatic metastases often emerge even during the course of successful liver-oriented treatment. In addition, an inadequately placed or malfunctioning catheter prevents efficient drug delivery [38]. Thus, catheter-related events such as occlusion, dislocation, and infection could result in interruption or termination of the treatment, even when the tumors are responding.

RFA has been attempted to treat selected patients with hepatic metastasis. The indication for RFA would include (1) liver-only disease; (2) size of the largest tumor less than

5 cm in diameter; and (3) location of tumor not adjacent to major vessels. RFA can be conducted either percutaneously under ultrasonic imaging guidance, laparoscopically, or by the open surgery approach. Reports on RFA applied to treat gastric cancer metastases to the liver remain scarce. Kim et al. [39] treated 20 patients by RFA or RFA and gastrectomy in case of synchronous metastases, achieving a median survival time of 30.7 months, whereas the experience by Kim et al. with 7 patients was more disappointing, with a median survival time of 11 months [40]. There is another report of 7 patients treated by HAIC followed by RFA who achieved a median survival time of 16.5 months [41]. This strategy was meant to select the patients so that RFA would only be delivered after confirming that new intrahepatic or systemic lesions do not develop during the HAIC. The chances of conducting a hepatectomy-versus-RFA trial for gastric cancer metastasis to the liver would seem unlikely. So far, the only clue of whether to perform hepatectomy or RFA comes from a meta-analysis of retrospective comparisons for colorectal liver metastases in which hepatectomy was significantly superior, even when conditions were limited to tumors >3 cm and solitary tumors [42]. Further prospective studies are needed to establish the position of RFA as an option for treatment of gastric liver metastases.

Conclusions

This working group reached the conclusion that hepatectomy could be considered in carefully selected cases of gastric cancer liver metastasis. The abstract of this article will appear in the forthcoming version of the Japanese gastric cancer treatment guidelines.

References

1. Shimada H, Tanaka K, Endou I, Ichikawa Y. Treatment for colorectal liver metastases: a review. Langenbecks Arch Surg. 2009;394:973–83.
2. Adam R, Chice L, Aloia T, Elias D, Salmon R, Rivoire M, et al. Hepatic resection for noncolorectal nonendocrine liver metastases. Analysis of 1425 patients and development of a prognostic model. Ann Surg. 2006;244:524–35.
3. Langley RR, Fidler IJ. The seed and soil hypothesis revisited: the role of tumor–stroma interactions in metastasis to different organs. Int J Cancer. 2011;128:2527–35.
4. Kodera Y, Ito S, Mochizuki Y, Yamamura Y, Misawa K, Ohashi N, et al. The number of metastatic lymph nodes is a significant risk factor for bone metastasis and poor outcome after surgery for linitis plastica-type gastric carcinoma. World J Surg. 2008;32:2015–20.
5. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines (ver. 3). Gastric Cancer. 2010;2011(14):113–23.
6. Takemura N, Saiura A, Koga R, Arita J, Yoshioka R, Ono Y, et al. Long-term outcomes after surgical resection for gastric cancer liver metastasis: an analysis of 64 macroscopically complete resections. Langenbecks Arch Surg. 2012;397:951–7.
7. Shirabe K, Shimada M, Matsumata T, Higashi H, Yakeishi Y, Wakiyama S, et al. Analysis of the prognostic factors for liver metastasis of gastric cancer after hepatic resection: a multi-institutional study of the indication for resection. Hepatogastroenterology. 2003;50:1560–3.
8. Wang Y-N, Shen K-T, Ling J-Q, Gao X-D, Hou Y-Y, Wang X-F, et al. Prognostic analysis of combined curative resection of the stomach and liver lesions in 30 gastric cancer patients with synchronous liver metastases. BMC Surg. 2012;12:20.
9. Cheon SH, Rha SY, Jeung HC, Im CK, Kim SH, Kim HR, et al. Survival benefit of combined curative resection of the stomach (D2 resection) and liver in gastric cancer patients with liver metastases. Ann Oncol. 2008;19:1146–53.
10. Makino H, Kunisaki C, Izumisawa Y, Tokuhisa M, Oshima T, Nagano Y, et al. Indication for hepatic resection in the treatment of liver metastasis from gastric cancer. Anticancer Res. 2010;30:2367–76.
11. Ambiru S, Miyazaki M, Ito H, Nakagawa K, Shimizu H, Yoshidome H, et al. Benefits and limits of hepatic resection for gastric metastases. Am J Surg. 2001;151:279–83.
12. Okano K, Maeba T, Ishimura K, Karasawa Y, Goda F, Wakabayashi H, et al. Hepatic resection for metastatic tumors from gastric cancer. Ann Surg. 2002;235:86–91.
13. Zacherl J, Zacherl M, Scheuba C, Steininger R, Wenzl E, Muhlbacher F, et al. Analysis of hepatic resection of metastasis originating from gastric adenocarcinoma. J Gastrointest Surg. 2002;6:682–9.
14. Sakamoto Y, Sano T, Shimada K, Esaki M, Saka M, Fukagawa T, et al. Favorable indications for hepatectomy in patients with liver metastasis from gastric cancer. J Surg Oncol. 2007;95:534–9.
15. Morise Z, Sugiokla A, Hoshimoto S, Kato T, Ikeda M, Uyama I, et al. The role of hepatectomy for patients with liver metastases of gastric cancer. Hepatogastroenterology. 2008;55:1238–41.
16. Thelen A, Jonas S, Benckert C, Lopez-Hanninen E, Neumann U, Rudolph B, et al. Liver resection for metastatic gastric cancer. Eur J Surg Oncol. 2008;34:1328–34.
17. Tsujimoto H, Ichikura T, Ono S, Sugasawa H, Hiraki S, Sakamoto N, et al. Outcomes for patients following hepatic resection of metastatic tumors from gastric cancer. Hepatol Int. 2010;4:406–13.
18. Miki Y, Fujitani K, Hirao M, Kurokawa Y, Mano M, Tsujie M, et al. Significance of surgical treatment of liver metastases from gastric cancer. Anticancer Res. 2012;32:665–70.
19. Garancini M, Uggeri F, Degrate L, Nespoli L, Gianotti L, Nespoli A, et al. Surgical treatment of liver metastases of gastric cancer: is local treatment in a systemic disease worthwhile? HPB (Oxf). 2012;14:209–15.
20. Schildberg CW, Croner R, Merkel S, Schellerer V, Muller V, Yedibela S, et al. Outcome of operative therapy of hepatic metastatic stomach carcinoma: a retrospective analysis. World J Surg. 2012;36:872–8.
21. Imamura H, Matsuyama Y, Shimada R, Kubota M, Nakayama A, Kobayashi A, et al. A study of factors influencing prognosis after resection of hepatic metastases from colorectal and gastric carcinoma. Am J Gastroenterol. 2001;96:3178–84.
22. Sarpel U, Bonavia AS, Grucela A, Roayaie S, Schwarz ME, Labow DM. Does anatomic versus nonanatomic resection affect recurrence and survival in patients undergoing surgery for colorectal liver metastasis? Ann Surg Oncol. 2009;16:379–84.
23. Ajani JA, Barthel JS, Bekaii-Saab T, Bentrem DJ, D'Amico TA, Das P, et al. Gastric cancer. J Natl Compr Canc Netw. 2010;8:378–409.
24. Wang Z, Chen J-Q. Imaging in assessing hepatic and peritoneal metastases of gastric cancer: a systemic review. BMC Gastroenterol. 2011;11:19.

25. Maas M, Rutten IJG, Nelemans PJ, Lambregts DM, Cappendijk VC, Beets GL, et al. What is the most accurate whole-body imaging modality for assessment of local and distant recurrent disease in colorectal cancer? A meta-analysis. Eur J Nucl Med Mol Imaging. 2011;38:1560–71.
26. Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol. 2011;29:4387–93.
27. Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, et al. Adjuvant vapecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet. 2012;379:315–21.
28. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355:11–20.
29. Li Z-Y, Tang L, Zhang L-H, Bu Z-D, Wu A-W, Wu X-J, et al. Weekly docetaxel and cisplatin plus fluorouracil as a preoperative treatment for gastric cancer with synchronous multiple hepatic metastasis: a pilot study. Med Oncol. 2010;27:1314–8.
30. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki 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;376:687–97.
31. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol. 2008;9:215–21.
32. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008;358:36–46.
33. Ohtsu A, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol. 2011;29:3968–76.
34. Narahara H, Ishii H, Imamura H, Tsuburaya A, Chin K, Imamoto H, et al. Randomized phase III study comparing the efficacy and safety of irinotecan plus S-1 with S-1 alone as first-line treatment for advanced gastric cancer (study GC0301/TOP-002). Gastric Cancer. 2011;14:72–80.
35. Yoshida M, Ohtsu A, Boku N, Miyata Y, Shirao K, Shimada Y, et al. Longterm survival and prognostic factors in patients with metastatic gastric cancers treated with chemotherapy in the Japan Clinical Oncology Group (JCOG) study. Jpn J Clin Oncol. 2004;34:654–9.
36. Kumada T, Arai Y, Itoh K, Takayasu Y, Nakamura K, Ariyoshi Y, et al. Phase II study of combined administration of 5-fluorouracil, epirubicin and mitomycin-C by hepatic artery infusion in patients with liver metastases of gastric cancer. Oncology. 1999;57:216–23.
37. Ojima H, Ootake S, Yokobori T, Mochida Y, Hosouchi Y, Nishida Y, et al. Treatment of multiple liver metastasis from gastric carcinoma. World J Surg Oncol. 2007;5:70.
38. Inaba Y, Arai Y, Matsueda K, Takeuchi Y, Aramaki T. Right gastric artery embolization to prevent acute gastric mucosal lesions in patients undergoing repeat hepatic arterial infusion chemotherapy. J Vasc Interv Radiol. 2001;12:957–63.
39. Kim HR, Cheon SH, Lee KH, Ahn JR, Jeung HC, Lee SS, et al. Efficacy and feasibility of radiofrequency ablation for liver metastases from gastric adenocarcinoma. Int J Hypertherm. 2010;26:305–13.
40. Kim HO, Hwang SI, Hong HP, Yoo CH. Radiofrequency ablation for metachronous hepatic metastases from gastric cancer. Surg Laparosc Endosc Percutan Tech. 2009;19:208–12.
41. Yamakado K, Nakatsuka A, Takaki H, Mori Y, Tonouchi H, Kusunoki M, et al. Prospective study of arterial infusion chemotherapy followed by radiofrequency ablation for the treatment of liver metastasis of gastric cancer. J Vasc Interv Radiol. 2005;16:1747–51.
42. Weng M, Zhang Y, Zhou D, Yang Y, Tang Z, Zhao M, et al. Radiofrequency ablation versus resection for colorectal cancer liver metastases: a meta-analysis. PLoS One. 2012;7:e45493.

Cancer Science
Japanese Cancer Association JCA
Open Access

Phase II trial of nanoparticle albumin-bound paclitaxel as second-line chemotherapy for unresectable or recurrent gastric cancer

Yasutsuna Sasaki,[1,2] Tomohiro Nishina,[3] Hirofumi Yasui,[4] Masahiro Goto,[5] Kei Muro,[6] Akihito Tsuji,[7] Wasaburo Koizumi,[8] Yasushi Toh,[9] Takuo Hara[10] and Yoshinori Miyata[11]

[1]Department of Medical Oncology, Saitama Medical University International Medical Center, Hidaka-shi; [2]Division of Medical Oncology, Department of Medicine, Showa University Hospital, Tokyo; [3]Department of Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama-shi; [4]Department of Gastrointestinal Oncology, Shizuoka Cancer Center, Nagaizumi-cho; [5]Cancer Chemotherapy Center, Osaka Medical College, Osaka; [6]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya; [7]Department of Clinical Oncology, Kochi Health Sciences Center, Kochi; [8]Department of Gastroenterology, Kitasato University, Sagamihara-shi; [9]Department of Gastroenterological Surgery, National Kyushu Cancer Center, Fukuoka; [10]Department of Surgery, Kouseiren Takaoka Hospital, Takaoka-shi; [11]Deparment of Gastroenterology, Saku Central Hospital, Nagano, Japan

Key words
Gastric cancer, *nab*-paclitaxel, phase II, second-line chemotherapy, triweekly

Yasutsuna Sasaki, Division of Medical Oncology, Department of Internal Medicine, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan.
Tel/Fax: +81-3-3783-8661
E-mail: yasutsuna@med.showa-u.ac.jp

Funding information
Taiho Pharmaceutical Co., Ltd.

Received January 5, 2014; Accepted April 8, 2014

Cancer Sci **105** (2014) 812–817

doi: 10.1111/cas.12419

This multicenter phase II study first investigated the efficacy and safety of nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel) when given every 3 weeks to patients with unresectable or recurrent gastric cancer who had received a prior round of fluoropyrimidine-containing chemotherapy. Patients with unresectable or recurrent gastric cancer who experienced progression despite fluoropyrimidine-containing treatment were studied. *Nab*-paclitaxel was given i.v. at 260 mg/m^2 on day 1 of each 21-day cycle without anti-allergic premedication until disease progression or study discontinuation. The primary endpoint was the overall response rate. The secondary endpoints were the disease control rate, progression-free survival, overall survival, and safety. From April 2008 to July 2010, 56 patients were enrolled, 55 patients received the study treatment, and 54 patients were evaluable for responses. According to an independent review committee, the overall response rate was 27.8% (15/54; 95% confidence interval [CI], 16.5–41.6) and the disease control rate was 59.3% (32/54; 95% CI, 45.0–72.4). One patient had a complete response. The median progression-free survival and overall survival were 2.9 months (95% CI, 2.4–3.6) and 9.2 months (95% CI, 6.9–11.4), respectively. The most common grade 3/4 toxicities were neutropenia (49.1%), leucopenia (20.0%), lymphopenia (10.9%), and peripheral sensory neuropathy (23.6%). There were no treatment-related deaths. *Nab*-paclitaxel, given every 3 weeks, showed promising activity against previously treated unresectable or recurrent gastric cancers, with well-tolerated toxicities. (Trial registration, ClinicalTrials.gov: NCT00661167).

Gastric cancer remains the second leading cause of cancer-related deaths worldwide[1] and is especially frequent in East Asia, including Japan.[2] Although surgical resection is the only curative treatment for gastric cancer, approximately 60% of patients eventually experience relapses after curative surgeries.[3] Globally, fluoropyrimidine-based combination chemotherapy regimens, including fluorouracil or its oral derivatives, taxanes, irinotecan, and platinum compounds, have yielded median progression-free survival (PFS) times of 2–7 months and median overall survival (OS) times of less than 1 year in first-line settings.[4–9] In Japan, the combination of S-1 (tegafur plus gimeracil plus oteracil potassium) and cisplatin is the most frequently prescribed first-line therapeutic regimen for patients with advanced/metastatic and recurrent gastric cancer. Recently, several phase III trials reported improved median OS times of more than 1 year.[10–12] Additionally, in a randomized European trial, irinotecan showed survival benefits, compared to best supportive care (BSC), as second-line treatment in gastric cancer patients after the failure of first-line chemotherapy.[13] A Korean study showed that docetaxel or irinotecan could also significantly prolong OS, compared with BSC, after one or two chemotherapeutic regimens that consisted of fluoropyrimidine and platinum.[14]

In Japan, paclitaxel (PTX) is commonly used as second-line chemotherapy for gastric cancer patients in practice, based on experiences with breast cancer and non-small-cell lung cancer (NSCLC). Paclitaxel yielded overall response rates (ORR) that ranged from 16 to 27%, overall OS times of 5–11 months, and modest toxicity in several phase II trials.[15–18]

The 130-nm nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel) is a novel, solvent polyoxyethylated castor oil (Cremophor)-free, biologically interactive form of PTX. *Nab*-paclitaxel is among the first of a new class of anticancer agents to incorporate albumin particle technology and exploit the unique properties of albumin, a natural carrier of lipophilic molecules in humans. *Nab*-paclitaxel allows the safe infusion of significantly higher doses of PTX than those used in standard PTX therapy, with shorter infusion schedules (30 min *vs* 3 h,

respectively) and no requirement of premedication for solvent-based hypersensitivity reactions. Additionally, in a preclinical study, *nab*-paclitaxel showed increased PTX transport across endothelial cells and greater antitumor activity, compared to standard PTX.[19] In phase III trials, *nab*-paclitaxel significantly increased the ORR and time to progression, compared to conventional PTX, in patients with metastatic breast cancer,[20] and significantly improved the ORR in advanced NSCLC patients, thus achieving the primary endpoint.[21]

We carried out the first phase II clinical trial to evaluate the efficacy and safety of *nab*-paclitaxel when given every 3 weeks to patients with unresectable or recurrent gastric cancer in whom treatment with one prior fluoropyrimidine-containing chemotherapeutic regimen failed.

Materials and Methods

Study objectives and design. This was a non-randomized, open-label, multicenter phase II registration trial of patients with unresectable or recurrent gastric cancer who had failed treatment with first-line chemotherapy (ClinicalTrials.gov, no. NCT00661167). The primary objective was the ORR, which was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, version 1.0.[22] The definition to confirmation of complete response (CR) and partial response (PR) required 4 weeks irrespective of study endpoints. The secondary objectives were PFS, OS, the disease control rate, and safety. This trial was carried out in accordance with Japanese guidelines on Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by the institutional review boards of all participating institutions.

Patients. Eligibility criteria for the study were: histologically confirmed adenocarcinoma of the stomach (regardless of human epidermal growth factor receptor 2 overexpression status); an age of 20–74 years; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; a history of progression or recurrence after one prior fluoropyrimidine-containing regimen (except for taxanes such as PTX and docetaxel); a life expectancy of ≥12 weeks; and adequate bone marrow (hemoglobin level ≥8.0 g/dL, white blood cell count ≤12 000/mm^3 or neutrophil count ≥1500/mm^3, and platelet count ≥100 000/mm^3), liver, and renal function (serum bilirubin level ≤1.5 times the upper limit of normal; aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels ≤2.5 times the upper limit of normal; and serum creatinine level ≤1.5 mg/dL). Presence of one or more measurable lesions, according to the RECIST criteria, was also a criterion. Patients were excluded if they had brain or wide-ranging bone metastases, malignant ascites, pleural or pericardial effusion that required drainage, peripheral neuropathy of grade 2 severity or worse according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (National Cancer Institute at the National Institutes of Health, Bethesda, MD, USA), a history of drug hypersensitivity, or severe complications such as uncontrolled infection, intestinal obstruction, or pulmonary fibrosis. Patients who required continuous steroid treatment and pregnant or nursing women were also excluded. Patients were not allowed to receive concomitant radiotherapy, other chemotherapy, immunotherapy, or targeted therapy during the trial. Written informed consent was obtained from all patients before enrolment.

Treatment. The baseline evaluations included imaging studies (computed tomography or MRI), a complete physical examination, pregnancy testing for female patients, an assessment of the ECOG PS, a complete blood count, serum chemical and electrolyte analyses, and urinalysis.

Nanoparticle albumin-bound paclitaxel was administered on an outpatient basis by a 30-min i.v. infusion at a PTX dose of 260 mg/m^2 on day 1 of each 21-day cycle; no steroid or antihistamine premedication or colony-stimulating factor support was given. Treatment was continued until disease progression, unacceptable toxicity, or consent withdrawal. Three dose reduction levels (220, 180, and 150 mg/m^2) were implemented under the dose reduction criteria. Complete blood counts, serum chemical analyses, and urinalyses were carried out weekly during the study.

Study assessment. The objective disease status was assessed according to the RECIST guidelines, version 1.0.[22] Imaging studies were repeated at least every 6 weeks after treatment initiation. Safety assessments, including serial history taking and physical examinations, and laboratory assessments were carried out throughout the study. The severity of adverse drug reactions (ADR) was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. An independent review committee that comprised radiologists and medical oncologists objectively confirmed treatment responses and drug-related adverse events.

Statistics. The primary measure of efficacy was the ORR. The ORR in previous phase II studies of PTX as second-line treatment for metastatic gastric cancer were 24%[15] and 27%.[16] The significant ORR threshold under the null hypothesis was defined as 10%, and the expected ORR under the alternative hypothesis was defined as 25%, based on a previous PTX report. If the ORR for *nab*-paclitaxel was 25%, a sample size of 53 patients would ensure a power of at least 80% for a one-sided significance level of 2.5% in order to reject the null hypothesis that the ORR was <10%. If the lower limit of the exact two-sided 95% confidence interval (CI), based on the ORR distribution, exceeded the 10% threshold, a response rate of 11 out of 53 patients would be met.

The disease control rate was defined as the sum of the percentages of CR, PR, and stable disease (SD) for ≥6 weeks. Overall survival was defined as the time between registration and death from any cause; PFS was defined as the time between registration and disease progression or death from any cause. Both OS and PFS were estimated using Kaplan–Meier curves.

All data obtained until the completion of the study period were included in the safety analyses. The primary efficacy analysis was based on the full analysis set of the patients. The safety analysis included all treated patients who received at least one dose of the experimental drug. The clinical cut-off date for this study was May 25, 2011.

Results

Fifty-six patients were enrolled at 10 centers in Japan between April 2008 and July 2010. One patient was ineligible because of inadequate prior treatment. Another patient was excluded from response evaluation because the initial treatment had been skipped due to rapid disease progression after registration. Fifty-five patients received the study treatment, and 55 and 54 patients were evaluable for safety and clinical response, respectively. Most of the patients were male (76.8%), and the median age was 63.5 years (Table 1). All treated patients had an ECOG PS of 0 or 1 (PS 0 = 58.9%; PS 1 = 41.1%). Thirty-five patients underwent gastrectomy. Twenty-one patients (37.5%)

Table 1. Baseline demographic and clinical characteristics of patients with unresectable or recurrent gastric cancer receiving nanoparticle albumin-bound paclitaxel as second-line therapy

	No. of patients (n = 56)	%
Gender		
Male	43	76.8
Female	13	23.2
Age, years		
Median	63.5	
Range	34–74	
ECOG PS		
0	33	58.9
1	23	41.1
Primary lesion		
Absent	35	62.5
Present	21	37.5
Type of treatment failure		
First line	40	71.4
Adjuvant	16	28.6
Number of metastatic organs		
1	19	33.9
2	22	39.3
≥3	15	26.8
Peritoneal metastasis		
Absent	35	62.5
Present	21	37.5
Metastatic organs (overlapping)		
Liver	30	53.6
Lung	8	14.3
Lymph node	37	66.1
Other	23	41.1
Adjuvant chemotherapy		
S-1	14	25.0
Others	3	5.4
First-line chemotherapy		
S-1-based	34	60.7
Capecitabine-based	5	8.9
Others	2	3.6

ECOG PS, Eastern Cooperative Oncology Group performance status; S-1, tegafur plus gimeracil plus oteracil potassium.

had peritoneal metastases. The most commonly prescribed prior chemotherapeutic agents were S-1 monotherapy as adjuvant treatment (25.0%) or S-1 in combination with cisplatin as first-line chemotherapy (35.7%). The total number of treatment cycles in the full analysis set population was 254. The median number of treatment cycles and relative dose intensity received per patient were 4 (range, 1–18), and 93.4% (range, 63.6–100.0%), respectively.

Overall responses in the 54 patients were reviewed and confirmed by the independent review committee (Table 2). One patient had a CR, 14 had PR, 17 had SD, and 21 had progressive disease. The ORR was 27.8% (95% CI, 16.5–41.6%), which exceeded the threshold response of 10% (Fig. 1). The median time to response was 36 days (range, 29–57 days).

The median PFS was 2.9 months (95% CI, 2.4–3.6 months), with a median follow-up time of 280 days (range, 46–1030 days; Fig. 2). The median survival time was 9.2 months (95% CI, 6.9–11.4 months) (Fig. 3). The median duration of treatment was 79.5 days (range, 22–477 days), with a median cumulative dose of 1574.5 mg (range, 387–6319 mg). Although 19 (34.5%) and 20 (36.4%) patients required dose

Table 2. Clinical responses of patients with unresectable or recurrent gastric cancer receiving nanoparticle albumin-bound paclitaxel as second-line therapy

	No. of patients (n = 54)	%
Complete response	1	1.9
Partial response	14	25.9
Stable disease	17	31.5
Progressive disease	21	38.9
Not evaluable	1	1.9
Overall response rate,%	27.8	
95% CI	16.5–41.6	
Disease control rate,%	59.3	
95% CI	45.0–72.4	
Progression-free survival, months		
Median	2.9	
95% CI	2.4–3.6	
Overall survival, months		
Median	9.2	
95% CI	6.9–11.4	

CI, confidence interval.

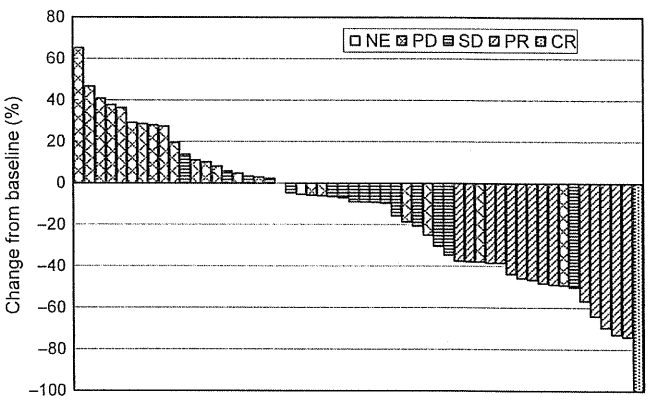

Fig. 1. Waterfall plot of the best overall response to nanoparticle albumin-bound paclitaxel as second-line therapy in the full analysis set of patients with unresectable or recurrent gastric cancer. CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

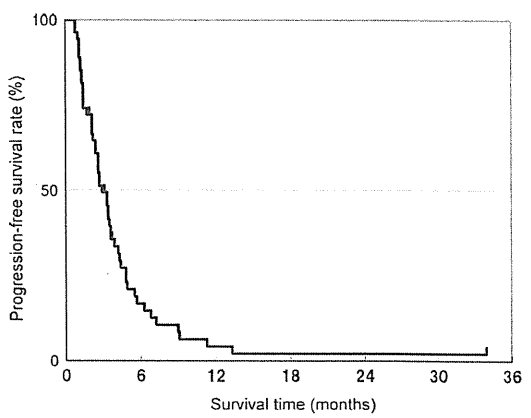

Fig. 2. Kaplan–Meier plots of progression-free survival in the full analysis set of patients with unresectable or recurrent gastric cancer receiving nanoparticle albumin-bound paclitaxel as second-line therapy.

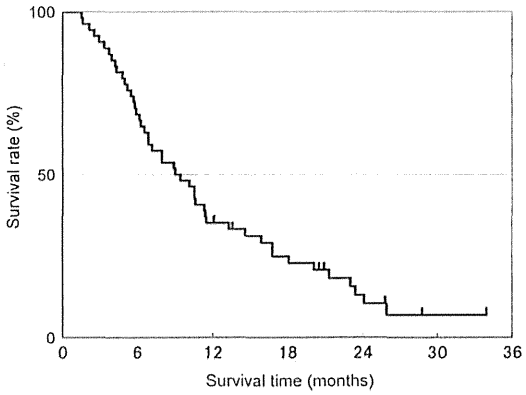

Fig. 3. Kaplan–Meier plots of overall survival in the full analysis set of patients with unresectable or recurrent gastric cancer receiving nanoparticle albumin-bound paclitaxel as second-line therapy.

reductions and delays, respectively, the mean relative dose intensity was 93.4% (range, 63.6–100.0%). Additional chemotherapy was given to the 44 (81.5%) patients in whom treatment with *nab*-paclitaxel failed, of whom, 37 (68.5%) received irinotecan-based chemotherapy (Table 3).

All patients were treated on an outpatient basis, and *nab*-paclitaxel was generally well tolerated. Safety was evaluated in the 55 patients who had received at least one dose of *nab*-paclitaxel. All patients reported at least one drug-related adverse event, but most adverse events were mild to moderate and well managed (Table 4). Although *nab*-paclitaxel was given without any premedication, no patients experienced hypersensitivity or acute infusion reactions. Grade 3 or 4 ADRs with incidence rates of >10% included neutropenia (49.1%), leucopenia (20.0%), lymphopenia (10.9%), and peripheral neuropathy (23.6%). No patients experienced febrile neutropenia in this study. The reasons for treatment withdrawal were mainly disease progression (87.0%) and toxicities (9.3%). There were no treatment-related deaths.

Discussion

Paclitaxel, a microtubule-stabilizing agent, is widely used to treat breast, lung, gastric, and ovarian cancers. However, the Cremophor-containing PTX formulation has been approved and prescribed worldwide because PTX is only slightly soluble in water. Premedication with steroids, antihistamines, and H_2 receptor blockers before the administration of Cremophor-based PTX is essential to reduce allergic, hypersensitivity, and anaphylactic reactions in the clinical setting. *Nab*-paclitaxel is a 130-nm nanoparticle albumin-bound paclitaxel formulation that is devoid of any solvents or ethanol. *Nab*-paclitaxel thus reduces the risk of hypersensitivity reactions and does not require steroid and antihistamine premedication; in fact, hypersensitivity reactions did not occur in this study. Additionally, because the *nab*-paclitaxel formulation does not contain alcohol, it can be administered to poor metabolizers of alcohol[23] and can prevent alcohol-induced hypersensitivity reactions. Furthermore, *nab*-paclitaxel can be given over a shorter time period (30 min) and without special i.v. tubing; therefore, polyethylene-lined i.v. bags composed of polyvinyl chloride can be used for its administration.[24,25] A comparative pharmacokinetic study of *nab*-paclitaxel and conventional PTX injections was carried out.[26] Patients with advanced solid tumors were randomly assigned to receive *nab*-paclitaxel (260 mg/m^2 i.v. over a 30-min period) or the conventional PTX injection (175 mg/m^2 i.v. over a 3-h period) every 3 weeks. The PTX clearance and distribution volumes were significantly higher in patients who received *nab*-paclitaxel than in those who received conventional PTX. Furthermore, Gardner *et al.* reported that the mean fraction of unbound PTX was consider-

Table 3. Subsequent treatment after the study chemotherapy (30-min i.v. infusion of 260 mg/m^2 nanoparticle albumin-bound paclitaxel every 3 weeks) in patients with unresectable or recurrent gastric cancer

	n = 54	%
Any	44	81.5
Irinotecan	29	53.7
Irinotecan + Cisplatin	8	14.8
Paclitaxel	3	5.6
Others†	4	7.4
None	10	18.5

†Other subsequent treatments include 5-fluorouracil/methotrexate (*n* = 2), everolimus or placebo (*n* = 1), and radiation (*n* = 1).

Table 4. Adverse events related to nanoparticle albumin-bound paclitaxel occurring in ≥10% of patients treated for unresectable or recurrent gastric cancer

Type	Grade				Grade 1–4	Grade 3–4
	1	2	3	4	*n* (%)	*n* (%)
Hematologic						
Anemia	3	12	3	1	19 (34.5)	4 (7.3)
Leukopenia	13	23	11	0	47 (85.5)	11 (20.0)
Neutropenia	0	16	18	9	43 (78.2)	27 (49.1)
Lymphopenia	2	13	5	1	21 (38.2)	6 (10.9)
Thrombocytopenia	9	0	0	0	9 (16.4)	0 (0.0)
Laboratory test abnormalities						
AST elevation	16	2	1	0	19 (34.5)	1 (1.8)
ALT elevation	17	3	0	0	20 (36.4)	0 (0.0)
ALP elevation	9	2	0	0	11 (20.0)	0 (0.0)
Hypoalbuminemia	10	3	0	0	13 (23.6)	0 (0.0)
Protein urine	4	4	0	0	8 (14.5)	0 (0.0)
Non-hematologic						
Constipation	5	1	1	0	7 (12.7)	1 (1.8)
Diarrhea	13	1	0	0	14 (25.5)	0 (0.0)
Nausea	19	1	1	0	21 (38.2)	1 (1.8)
Stomatitis	15	3	0	0	18 (32.7)	0 (0.0)
Vomiting	4	1	1	0	6 (10.9)	1 (1.8)
Asthenia	10	6	0	0	16 (29.1)	0 (0.0)
Fatigue	1	8	1	0	10 (18.2)	1 (1.8)
Malaise	7	3	0	0	10 (18.2)	0 (0.0)
Pyrexia	7	3	0	0	10 (18.2)	0 (0.0)
Weight decreased	4	1	1	0	6 (10.9)	1 (1.8)
Anorexia	19	9	1	0	29 (52.7)	1 (1.8)
Arthralgia	16	1	3	0	36 (65.5)	3 (5.5)
Myalgia	16	16	3	0	35 (63.6)	3 (5.5)
Peripheral motor neuropathy	6	3	1	0	10 (18.2)	1 (1.8)
Peripheral sensory neuropathy	20	18	13	0	51 (92.7)	13 (23.6)
Alopecia	37	15	NA	NA	52 (94.5)	NA
Pruritus	11	1	0	NA	12 (21.8)	0 (0.0)
Rash	10	1	0	0	11 (24.4)	0 (0.0)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not applicable.

ably higher with *nab*-paclitaxel than with conventional PTX.[27] This pharmacokinetic property of *nab*-paclitaxel might be associated with higher PTX distribution to the tumor. Additionally, in preclinical studies, PTX transport across the endothelium was enhanced by albumin receptor-mediated transcytosis, and PTX delivery to tumors might be enhanced by the binding of albumin-bound PTX to interstitial albumin-binding proteins such as secreted protein acidic and rich in cysteine.[28] In a preclinical model and at equitoxic doses, the *nab*-paclitaxel-treated groups showed more complete regression, a longer time to recurrence, a longer doubling time, and prolonged survival, compared to the Cremophor-containing PTX-treated group.[19] *Nab*-paclitaxel without premedication showed significantly higher response rates and a longer time to tumor progression than PTX or docetaxel in advanced or recurrent breast cancer patients.[20,29] Additionally, weekly *nab*-paclitaxel plus carboplatin-based therapy resulted in a significantly improved ORR in advanced NSCLC patients, compared to that associated with PTX plus carboplatin, with a trend toward improved OS and PFS.[21] And in patients with metastatic pancreatic adenocarcinoma, *nab*-paclitaxel plus gemcitabine significantly improved OS, PFS, and ORR without life-threatening toxicities, which could make this treatment the standard treatment.[30]

Gastric cancer remains one of the most important malignancies, especially in Asian countries. Several phase III studies demonstrated a significantly prolonged OS in patients with advanced or recurrent gastric cancer in response to first-line fluoropyrimidine-based chemotherapies.[7,10,31] Paclitaxel at a dose of 210 mg/m^2, repeated every 3 weeks, was initially evaluated in Japan and yielded an objective PR rate of 28% in a registration trial of untreated or minimally treated gastric cancer patients. Several small-scale phase II studies of weekly-administered PTX reported response rates ranging from 16% to 24%[15,17] for gastric cancer patients in a second-line setting (Table 5). Furthermore, as it resulted in a better survival benefit than irinotecan in the West Japan Oncology Group WJOG4007 trial, weekly PTX could be adopted as a control arm in future phase III trials of second-line chemotherapy for gastric cancer.[32] Based on these clinical trials, weekly PTX has become the most frequently prescribed second-line drug in Japan.

This phase II study of *nab*-paclitaxel is the first phase II trial for the treatment of advanced or recurrent gastric cancer. No significant hypersensitivity or anaphylactic reactions were induced by *nab*-paclitaxel without premedication. The main reason for treatment discontinuation was disease progression, and two patients discontinued the study treatment because of adverse events, which included thrombosis and peripheral sensory neuropathy. No new safety concerns related to *nab*-paclitaxel or conventional PTX were identified, and there were no treatment-related deaths in this study. Although grade 3/4 toxicities such as neutropenia, leucopenia, and lymphopenia were observed, these ADRs were clinically well managed. Grade 3 peripheral sensory neuropathy remains an important problem that might be controlled by dose reductions and delays before the symptoms worsen. The clinical responses and PFS with *nab*-paclitaxel as second-line treatment seem comparable to those obtained in prior PTX trials, although no direct comparison data with PTX are available (Table 5). Recently, survival advantages were reported for irinotecan versus BSC and for irinotecan or docetaxel versus BSC as second-line treatment for gastric cancer patients.[13,14] Weekly PTX failed to show a survival advantage over irinotecan in a phase III trial.[32]

In conclusion, *nab*-paclitaxel, when given every 3 weeks, shows promising activity and well-tolerated toxicities in patients with previously treated unresectable or recurrent gastric cancer. A phase III trial is ongoing to evaluate the clinical benefit of *nab*-paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer (JapicCTI-132059).

Table 5. Second-line treatments for gastric cancer

Regimen	No. of patients	RR (%)	MST (days)	PFS (days)	Reference
Weekly paclitaxel (80 mg/m^2)	25	24	151	64	15
Weekly paclitaxel (80 mg/m^2)	44	16	237	79	17
Biweekly paclitaxel (140 mg/m^2)	40	17.5	254	111	34
Triweekly paclitaxel (210 mg/m^2)	26	27	319	NA	16
Triweekly paclitaxel (210 mg/m^2)	15	20.0	NA	NA	18
Triweekly docetaxel (75 mg/m^2)	49	16.3	252	76	33
This trial	54	27.8	279	88	NA

MST, median survival time; NA, not applicable; PFS, progression-free survival; RR, response rate.

Acknowledgments

We are grateful to Drs. Hiroya Takiuchi, Toru Sasaki, Satoshi Tanabe, Mizutomo Azuma, Akihisa Tomori, Yusuke Onozawa, Akira Fukutomi, Kentaro Yamazaki, Takeshi Sakamoto, Kohei Shitara, Tomoya Yokota, Motoki Yoshida, Shinichiro Hori, Takeshi Kajiwara, Junichiro Nasu, Eiji Oki, Keishi Yamashita, Hiroo Ishida, Yu Sunakawa, Keiko Mizuno, Ken Shiozawa, Atsushi Sato, Junji Tanaka, Hiroki Yoshikawa, Hiroshi Ariyoshi, Yusuke Tanigawara, Keisuke Aiba, and Nagahiro Saijo for their important contributions to this trial. This trial was supported by Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan).

Disclosure Statement

Y.S. received lecture fees from Taiho Pharmaceutical Co., Ltd. The authors report no other potential conflicts of interest relevant to this article. Taiho Pharmaceutical Co., Ltd., a designer of the study, had funded the study and also collected and analyzed the data contributed to interpretation of the study. All authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

References

1 International Agency for Research on Cancer. GLOBOCAN 2008: Estimated cancer Incidence, Mortality, Prevalence and Disability-adjusted life years (DALYs) Worldwide in 2008. [Cited 9 Nov 2013.] Available from URL: http://globocan.iarc.fr/.
2 Center for Cancer Control and Information Services, National Cancer Center. Cancer Statistics in Japan-2012. [Cited 15 Jan 2013.] Available from URL: http://ganjoho.jp/pro/statistics/en/backnumber/2012_en.html.
3 Menges M, Hoehler T. Current strategies in systemic treatment of gastric cancer and cancer of the gastroesophageal junction. *J Cancer Res Clin Oncol* 2009; **135**: 29–38.
4 Ohtsu A, Shimada Y, Shirao K *et al.* Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: the Japan Clinical Oncology Group Study (JCOG9205). *J Clin Oncol* 2003; **21**: 54–9.
5 Dank M, Zaluski J, Barone C *et al.* Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced ade-

nocarcinoma of the stomach or esophagogastric junction. *Ann Oncol* 2008; **19**: 1450–7.
6 Kang YK, Kang WK, Shin DB *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**: 666–73.
7 Van Cutsem E, Moiseyenko VM, Tjulandin S *et al.* Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006; **24**: 4991–7.
8 Bolke E, Peiper M, Budach W. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008; **358**: 1965; author reply 1965.
9 Al-Batran SE, Hartmann JT, Probst S *et al.* Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol* 2008; **26**: 1435–42.
10 Koizumi W, Narahara H, Hara T *et al.* S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008; **9**: 215–21.
11 Boku N, Yamamoto S, Fukuda H *et.al.* Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. *Lancet Oncol* 2009; **10**: 1063–9.
12 Narahara H, Iishi H, Imamura H *et al.* Randomized phase III study comparing the efficacy and safety of irinotecan plus S-1 with S-1 alone as first-line treatment for advanced gastric cancer (study GC0301/TOP-002). *Gastric Cancer* 2011; **14**: 72–80.
13 Thuss-Patience PC, 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). *Eur J Cancer* 2011; **47**: 2306–14.
14 Kang JH, Lee SI, Lim DH *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; **30**: 1513–8.
15 Hironaka S, Zenda S, Boku N, Fukutomi A, Yoshino T, Onozawa Y. Weekly paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer. *Gastric Cancer* 2006; **9**: 14–8.
16 Yamada Y, Shirao K, Ohtsu A *et al.* Phase II trial of paclitaxel by three-hour infusion for advanced gastric cancer with short premedication for prophylaxis against paclitaxel-associated hypersensitivity reactions. *Ann Oncol* 2001; **12**: 1133–7.
17 Kodera Y, Ito S, Mochizuki Y *et al.* A phase II study of weekly paclitaxel as second-line chemotherapy for advanced gastric Cancer (CCOG0302 study). *Anticancer Res* 2007; **27**: 2667–71.
18 Yamaguchi K, Tada M, Horikoshi N *et al.* Phase II study of paclitaxel with 3-h infusion in patients with advanced gastric cancer. *Gastric Cancer* 2002; **5**: 90–5.
19 Desai N, Trieu V, Yao Z *et al.* Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel. *Clin Cancer Res* 2006; **12**: 1317–24.
20 Gradishar WJ, Tjulandin S, Davidson N *et al.* Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol* 2005; **23**: 7794–803.
21 Socinski MA, Bondarenko I, Karaseva NA *et al.* Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. *J Clin Oncol* 2012; **30**: 2055–62.
22 Therasse P, Arbuck SG, Eisenhauer EA *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**: 205–16.
23 Goedde HW, Agarwal DP, Fritze G *et al.* Distribution of ADH2 and ALDH2 genotypes in different populations. *Hum Genet* 1992; **88**: 344–6.
24 Ibrahim NK, Desai N, Legha S *et al.* Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. *Clin Cancer Res* 2002; **8**: 1038–44.
25 Nyman DW, Campbell KJ, Hersh E *et al.* Phase I and pharmacokinetics trial of ABI-007, a novel nanoparticle formulation of paclitaxel in patients with advanced nonhematologic malignancies. *J Clin Oncol* 2005; **23**: 7785–93.
26 Sparreboom A, Scripture CD, Trieu V *et al.* Comparative preclinical and clinical pharmacokinetics of a cremophor-free, nanoparticle albumin-bound paclitaxel (ABI-007) and paclitaxel formulated in Cremophor (Taxol). *Clin Cancer Res* 2005; **11**: 4136–43.
27 Gardner ER, Dahut WL, Scripture CD *et al.* Randomized crossover pharmacokinetic study of solvent-based paclitaxel and nab-paclitaxel. *Clin Cancer Res* 2008; **14**: 4200–5.
28 Desai NTV, Yao R, Frankel T, Soon-Shiong P. SPARC expression in breast tumors may correlate to increased tumor distribution of nanoparticle albumin-bound paclitaxel (ABI-007) vs Taxol. *Breast Cancer Res Treat* 2004; **88**: S26–7.
29 Gradishar WJ, Krasnojon D, Cheporov S *et al.* Significantly longer progression-free survival with nab-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer. *J Clin Oncol* 2009; **27**: 3611–9.
30 Von Hoff DD, Ervin T, Arena FP *et al.* Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369**: 1691–703.
31 Bang YJ, 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**: 687–97.
32 Hironaka S, Ueda S, Yasui H *et al.* Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. *J Clin Oncol* 2013; **31**: 4438–44.
33 Lee J-L, Ryu M-H, Chang HM, *et al.* A phase II study of docetaxel as salvage chemotherapy in advanced gastric cancer after failure of fuoropyrimidine and platinum combination chemotherapy. *Cancer Chemother Pharmacol* 2008; **61**: 631–637.
34 Koizumi W, Akiya T, Sato A, *et al.* Second-line chemotherapy with biweekly paclitaxel after failure of fluoropyrimidine-based treatment in patients with advanced or recurrent gastric vancer: a report from the Gastrointestinal Oncology Group of the Tokyo Cooperative Oncology Group, TCOG GC-0501 Trial. *Jpn J Clin Oncol* 2009; **39**: 713–719.

Int J Clin Oncol (2014) 19:656–661
DOI 10.1007/s10147-013-0610-1

ORIGINAL ARTICLE

Long-term outcomes and prognostic factors of patients with advanced gastric cancer treated with S-1 plus cisplatin combination chemotherapy as a first-line treatment

Shigenori Kadowaki · Azusa Komori · Yukiya Narita · Sohei Nitta · Kazuhisa Yamaguchi · Chihiro Kondo · Hiroya Taniguchi · Daisuke Takahari · Takashi Ura · Masashi Ando · Kei Muro

Received: 12 June 2013 / Accepted: 10 August 2013 / Published online: 3 September 2013

Abstract
Background The long-term outcomes of advanced gastric cancer (AGC) patients treated with S-1 plus cisplatin (SP) combination chemotherapy remain unclear. Therefore, we sought to evaluate these outcomes to identify the prognostic factors affecting patient survival.
Methods We retrospectively analyzed 153 AGC patients treated with SP at a single institution between January 2005 and July 2011.
Results Median overall survival (OS) was 15.0 months [95 % confidence interval (CI), 12.5–17.9 months]. Three independent prognostic factors affecting poor survival were identified: performance status (PS) ≥ 1 [hazard ratio (HR) = 2.39, 95 % CI, 1.58–3.62]; >1 metastatic site (HR = 1.57, 95 % CI, 1.10–2.26], and elevated alkaline phosphatase levels (HR = 1.70, 95 % CI, 1.16–2.49). A simple prognostic index was generated using three risk groups: good (no risk factor), moderate (one or two risk factors), and poor (three risk factors). The median OS for good-, moderate-, and poor-risk groups was 28.6, 14.8, and 7.3 months, respectively (log-rank test; $P < 0.0001$). Among the twelve 3-year survivors, 9 (75 %) had a PS of 0 and 8 (67 %) had only one metastatic site.
Conclusions Three prognostic factors were identified in AGC patients treated with SP. Using a simple prognostic index, the patients were divided into three risk groups, in which the survival differences were markedly significant, suggesting that patients with good PS and only one metastatic site may have a higher chance of long-term survival than those with poor PS and multiple metastatic sites.

Keywords Gastric cancer · S1 plus cisplatin chemotherapy · Prognostic factors · Long-term survival

Introduction

Among malignant tumors, gastric cancer is the second leading cause of death worldwide [1]. Although the mortality rate associated with gastric cancer is decreasing, this disease claims approximately 50,000 lives in Japan every year. Several randomized trials have revealed that overall survival (OS) in advanced gastric cancer (AGC) is improved with systemic chemotherapy compared with the best supportive care [2–4]; however, several recent phase III trials reported that the prognosis for AGC remained poor, with a median survival time of 9.2–13.0 months [5–7]. In AGC, the outcome of systemic chemotherapy depends on patient and tumor characteristics. Recently studies have shown that poor performance status (PS) [8–13], multiple metastatic sites [11–13], peritoneal metastasis [9, 13], bone metastasis [8, 13], liver metastasis [9], no prior gastrectomy [8, 10], and elevated alkaline phosphatase (ALP) levels [9] were independent prognostic factors of poor OS.

A randomized phase III trial conducted by the Japan Clinical Oncology Study Group (JCOG) demonstrated that OS after S-1 (an oral fluoropyrimidine) monotherapy was not inferior to that after infused 5-fluorouracil (5-FU) [14]. Furthermore, a phase III trial of S-1 alone versus S-1 plus cisplatin in a randomized controlled trial in the treatment of

S. Kadowaki (✉) · A. Komori · Y. Narita · S. Nitta · K. Yamaguchi · C. Kondo · H. Taniguchi · D. Takahari · T. Ura · M. Ando · K. Muro
Department of Clinical Oncology, Aichi Cancer Center Hospital, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, Aichi 464-8681, Japan
e-mail: skadowaki@aichi-cc.jp

stomach cancer (SPIRITS) demonstrated that S-1 plus cisplatin (SP) was superior to S-1 [7]. A phase III First-Line Advanced Gastric Cancer Study conducted mainly among Western countries demonstrated that SP was not inferior to 5-FU plus cisplatin, with SP having lower toxicities [15]. On the basis of these results, SP combination chemotherapy was established as a standard first-line treatment for AGC in Japan. In clinical settings, however, little is known regarding the prognostic factors and long-term outcomes of AGC patients treated with SP. Hence, the aim of the present retrospective study was to analyze the prognostic factors affecting OS and to evaluate the characteristics of long-term survival in AGC patients treated with SP as a first-line treatment in a clinical setting.

Materials and methods

Patients and treatment schedule

The present retrospective study analyzed the outcomes of 153 AGC patients treated with SP as first-line chemotherapy between January 2005 and July 2011 at the Aichi Cancer Center Hospital (Aichi, Japan). All patients were diagnosed with histologically confirmed inoperable adenocarcinoma. Most patients received SP according to a standard schedule (S-1 at 80 mg/m^2 per day for 3 weeks followed by a 2-week rest; cisplatin at 60 mg/m^2 intravenous infusion on day 8; 5-week cycles). Only 7 patients received SP in a thrice-weekly schedule (S-1 at 80 mg/m^2 per day for 2 weeks followed by a 1-week rest; cisplatin at 60 mg/m^2 intravenous infusion on day 1; 3-week cycles). Treatment was continued until disease progression, intolerable toxicity, or patient refusal. Tumor response was assessed on the basis of the Response Evaluation Criteria in Solid Tumors version 1.0 [16]. Confirmation of treatment response was not required for this study. Written informed consent was obtained from all patients before administration of the first-line treatment.

Statistical analysis

Progression-free survival (PFS) was calculated from the date of SP initiation to the date of disease progression or death from any cause, whichever occurred first. OS was calculated from the date of SP initiation to the date of death from any cause. PFS and OS were estimated using the Kaplan–Meier method. Of the 153 patients, 6 (4 %) were lost to follow-up. Survival status was updated in April 2013. Univariate analyses were performed using the log-rank test with the following variables: (1) age (<65 vs. ≥65 years); (2) gender (male vs. female); (3) Eastern Cooperative Oncology Group performance status (ECOG PS) (0 vs. 1–2); (4) histology (diffuse vs. intestinal type); (5) peritoneal metastasis (no vs. yes); (6) liver metastasis (no vs. yes); (7) lymph node metastasis (no vs. yes); (8) number of metastatic sites (1 vs. ≥2); (9) history of gastrectomy (no vs. yes); and (10) ALP levels (normal vs. high). A multivariate analysis of prognostic factors using the stepwise Cox proportional hazard model was performed with these categorical variables to calculate the hazard ratio (HR) and associated 95 % confidence intervals (CIs). A two-sided P value less than 0.05 was considered statistically significant. All statistical calculations were performed using Dr. SPSS II software (SPSS Japan, Tokyo, Japan).

Results

Patient characteristics

Pretreatment patient characteristics are summarized in Table 1. As shown, the median patient age was 62.0 years (range 28–83 years), and 91 (60 %) were men. Among the 153 patients, 102 did not undergo gastrectomy before initial chemotherapy because of unresectable disease, 20 underwent resection of the primary site but had residual disease, and 31 had recurrent disease after previous curative gastrectomy. Of the 102 patients who had initially unresectable disease, 2 underwent curative surgery after achieving a good response with the first-line treatment and 1 underwent palliative gastrectomy for pyloric stenosis. A total of 120 (78 %) patients received second-line chemotherapy: 75 (63 %), 32 (27 %), and 13 (11 %) received taxane-based regimens, irinotecan-based regimens, and other, respectively. Only 2 (1 %) patients were actively receiving SP as the first-line treatment at the time of this analysis.

Tumor response and survival

The overall response rates are summarized in Table 2. Of the 94 patients with measurable disease, 5 (5 %) were not evaluated for unacceptable toxicities or clinical disease progression. The overall response rate was 41 % (95 % CI, 31–52 %); 2 (2 %) patients achieved complete response and 37 (39 %) achieved partial response. The median follow-up period was 26.8 months (range 4.9–69.5 months), the median PFS was 5.9 months (95 % CI, 5.0–6.8 months), and the median OS was 15.0 months (95 % CI, 12.5–17.9 months) (Fig. 1a, b). The 1-, 2-, and 3-year survival rates were 61, 29, and 12 %, respectively.

Table 1 Patient characteristics

Characteristic	$n = 153$	Percent (%)
Age, years		
Median (range)	62.0 (28–83)	
Gender		
Male	91	59
Female	62	41
ECOG PS		
0	48	31
1	98	64
2	7	5
Histological type		
Diffuse type	113	74
Intestinal type	40	26
Disease status		
Unresectable	122	80
Recurrent	31	20
Prior gastrectomy		
Yes	51	33
No	102	67
Metastatic sites		
Peritoneum	92	60
Lymph node	84	55
Liver	33	22
Bone	14	9
Lung	12	8
Number of metastatic sites		
1	76	50
2	55	36
≥3	22	14

ECOG Eastern Cooperative Oncology Group, *PS* performance status

Table 2 Tumor response in patients with measurable lesions

Response	$n = 94$	%
CR	2	2
PR	37	39
SD	30	32
PD	20	21
NE	5	5

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable

Analysis of prognostic factors

The results of univariate survival analysis are listed in Table 3. PS, peritoneal metastasis, number of metastatic sites, prior gastrectomy, and elevated ALP levels significantly affected OS. Patients with ECOG PS grade 0 had better OS than those with ECOG PS grades 1 or 2 ($P < 0.0001$). Patients with only one metastatic site had better OS compared with those with multiple metastatic sites ($P = 0.003$). Multivariate analyses showed that PS ≥ 1 (HR, 2.39; 95 % CI, 1.58–3.62; $P < 0.001$), multiple metastatic sites (HR, 1.57; 95 % CI, 1.10–2.26; $P = 0.014$), and elevated ALP levels (HR, 1.70; 95 % CI, 1.16–2.49; $P = 0.007$) were independent prognostic factors (Table 4) that were observed in almost all patients, although ALP data were unavailable in one patient. All three factors had similar orders of magnitude in all patients, and those with one ($n = 53$) or two ($n = 51$) prognostic factors had similar OS (log-rank test, $P = 0.46$; 15.9 vs. 12.8 months and 66 vs. 62 % for median survival time and 1-year survival rate, respectively). Therefore, we categorized patients into prognostic risk groups as follows: patients with no prognostic factor as the good-risk group ($n = 25$), those with one or two prognostic factors as the moderate-risk group ($n = 104$), and those with three

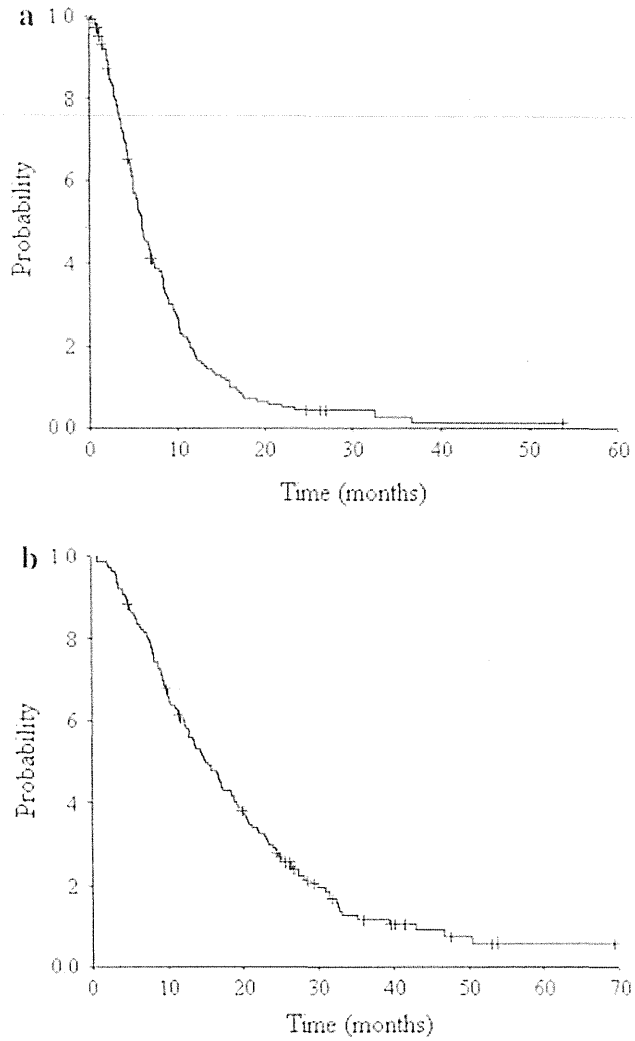

Fig. 1 **a**, **b** Kaplan–Meier survival curves of progression-free survival (PFS) and overall survival (OS) for all patients ($n = 153$). **a** Median PFS was 5.9 months (95 % CI, 5.0–6.8 months). **b** Median OS was 15.0 months (95 % CI, 12.5–17.9 months)

Table 3 Univariate prognostic factor analysis for overall survival

Variable	*n*	Median OS (months)	*P* value
Age (years)			
<65	92	13.7	0.15
≥65	61	18.5	
Gender			
Male	91	14.8	0.21
Female	62	15.8	
Performance status			
0	48	27.4	<0.0001
≥1	105	12.3	
Histology			
Diffuse	113	15.8	0.60
Intestinal	40	14.3	
Metastatic sites			
Peritoneum			
−	61	17.1	0.01
+	92	14.3	
Liver			
−	120	15.8	0.68
+	33	13.8	
Lymph node			
−	69	15.9	0.27
+	84	14.3	
Bone			
−	139	15.5	0.07
+	14	12.8	
Lung			
−	141	15.0	0.30
+	12	17.3	
Number of metastatic sites			
1	76	19.9	0.003
≥2	77	12.6	
Prior gastrectomy			
No	102	12.8	0.001
Yes	51	21.2	
ALP[a]			
Normal	109	17.3	0.0004
High	43	10.5	

OS overall survival, *ALP* alkaline phosphatase

[a] No measurement in one patient

Table 4 Multivariate analysis of overall survival using the stepwise Cox's model

	Hazard ratio	95 % CI	*P* value
Performance status	2.39	1.58–3.62	<0.001
Number of metastatic sites	1.57	1.10–2.26	0.014
ALP	1.70	1.16–2.49	0.007

CI confidence interval

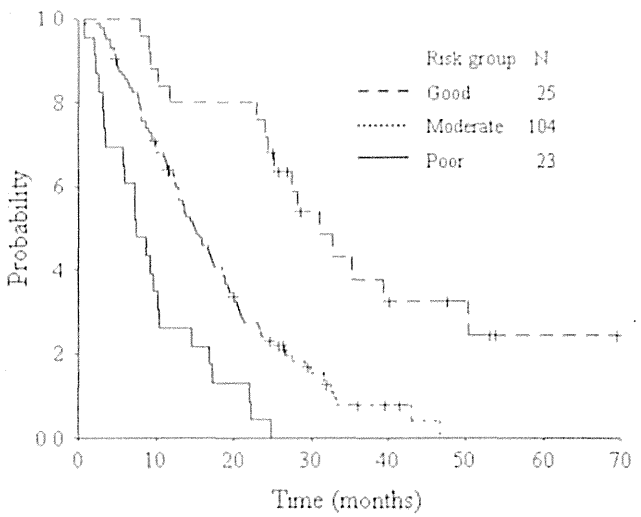

Fig. 2 Overall survival curves by prognostic index. Median survival time for the good-risk (*dashed line*), moderate-risk (*dotted line*), and poor-risk (*solid line*) groups were 28.6, 14.8, and 7.3 months, respectively, and the 3-year survival rate was 38, 8, and 0 %, respectively

prognostic factors as the poor-risk group ($n = 23$). Figure 2 shows the overall survival curves for these three risk groups. There were significant differences in OS among the three risk groups (log-rank test, $P < 0.0001$). The median survival time for the good-, moderate-, and poor-risk groups was 28.6, 14.8, and 7.3 months, respectively, and the 3-year survival rate was 38, 8, and 0 %, respectively. We found that the moderate-risk group had a 3.1-fold-increased risk of death (HR, 3.12; 95 % CI, 1.78–5.47; $P < 0.001$) and that the poor-risk group had a 7.9-fold-increased risk of death (HR, 7.93; 95 % CI, 3.99–15.76; $P < 0.001$) compared with the good-risk group. The median PFS for the good-, moderate-, and poor-risk groups was 9.7, 5.7, and 3.2 months, with significant differences (log-rank test, $P = 0.001$). Of patients who received taxanes and irinotecan as subsequent therapy, 19 (76 %) and 15 (60 %) were in the good-risk group, 71 (68 %) and 44 (42 %) in the moderate-risk group, and 13 (57 %) and 7 (30 %) in the poor-risk group, respectively.

Characteristics of long-term survivors

Characteristics of the 12 patients who survived more than 3 years are summarized in Table 5. Nine (75 %) of the 12 patients had a PS of 0, and 8 (67 %) had prior gastrectomy. Eight (67 %) patients had only one metastatic site and 3 (25 %) achieved a complete response (CR); 1 patient achieved CR following first-line chemotherapy and 2 achieved CR following second-line chemotherapy.

Table 5 Characteristics of 3-year survivors

Age (years)	G	PS	PGA	MS	Response		PFS	Risk group	Survival	Status
					1st	2nd				
41	F	1	No	P, LN	SD	NE	13.2	Moderate	36.1	A
57	F	0	Yes	P	IR/SD	NE	4.4	Good	39.4	D
66	F	1	No	LN	PR	PR	5.7	Moderate	39.5	A
73	F	0	Yes	Li	SD	PR	10.0	Good	40.6	D
72	M	0	No	LN, Lu	PR	PR	9.9	Moderate	41.4	A
71	F	1	Yes	P, LN	PR	SD	11.3	Moderate	42.9	D
68	M	0	No	LN, Li, Lu	PR	PR	19.0	Moderate	46.7	D
70	F	0	Yes	Lu	PR	CR	3.9	Good	47.6	A
70	M	0	Yes	LN	SD	SD	8.3	Good	50.4	D
65	M	0	Yes	LN	PR	SD	36.7	Good	53.0	A
61	F	0	Yes	Li	CR	–	53.8	Good	53.8	A, NED
55	F	0	Yes	P	IR/SD	CR	20.3	Good	69.5	A, NED

G gender, *M* male, *F* female, *PS* performance status, *PGA* prior gastrectomy, *MS* metastatic site, *P* peritoneum, *LN* lymph node, *Li* liver, *Lu* lung, *NE* not evaluable, *PFS* progression-free survival, *A* alive, *D* dead, *NED* no evidence of disease

The median PFS (10.7 months; range 3.9–53.8 months) in the 3-year survivors was longer than that in the entire population. Seven patients were alive during the follow-up period, of which 4 were classified in the good-risk group.

Discussion

In the present study, we retrospectively investigated the prognostic factors and long-term outcomes of AGC patients treated with SP at a single institution. We found that PS ≥1, multiple metastatic sites, and elevated ALP levels were prognostic factors of decreased OS. Using these factors, we developed a simple prognostic index to classify patients into three risk groups.

Consistent with previous studies [8–13], we found that PS was an independent predictor of OS and only one metastatic site was an independent prognostic factor of improved OS. This finding is also consistent with several other reports [11–13]. In two Korean studies, initial metastatic state (no prior gastrectomy) was a significant prognostic factor of poor survival [8, 10]. One reasonable explanation for these results is that multiple metastatic sites and initial metastatic state may reflect larger tumor volumes; however, metastatic sites such as the liver, peritoneum, and bone were not significantly associated with OS, suggesting that tumor volume may be a more important prognostic variable than metastatic lesions in the outcome of AGC patients treated with chemotherapy. Consistent with the findings of Chau et al. [9], we determined that elevated ALP level was a prognostic factor of poor OS; however, this association was unclear in our series.

Our simple prognostic model identified three different risk groups, and because all three prognostic factors can easily be evaluated before treatment, it can help clinicians and patients make clinical treatment decisions and help in further research regarding risk stratification in AGC. To date, several prognostic models have been developed to predict the outcome of AGC patients treated with palliative chemotherapy [8, 9, 13, 17]. However, in the prognostic index validated by Chau et al. [9], 27 % of the included patients had esophageal cancer and 22 % had locally advanced disease. In the report by the Korean group, a prognostic model developed using a training set of 1,870 patients was validated in sets of 935 AGC patients [17]. This model had good applicability to AGC patients who received a 3-week SP regimen [8], whereas the more complex model comprised eight prognostic factors and therefore may not be useful in clinical application. Our proposed index has not been validated and has several limitations inherent to retrospective analyses, but proposes information valuable to clinical practice and will be worthy of validation in future.

In the present study, the median PFS and OS of patients receiving SP were 5.9 and 15.0 months, which were similar to those observed in the SPIRITS trial (median PFS and OS, 6.0 and 13.0 months, respectively) [7]. Regarding patient background, a higher proportion of our patients had poorer PS (ECOG PS ≥ 1; 69 vs. 28 %), peritoneal metastasis (60 vs. 34 %), and only one metastatic site (50 vs. 28 %). The proportion of our patients receiving second-line chemotherapy in the present study was approximately equal to that in the SPIRITS trial (78 vs. 74 %). The median OS of patients with peritoneal metastasis was 14.3 months, similar to that in the entire population. The

decrease in survival, indicated by poorer PS, may be counteracted by the small number of involved organs involved.

To our knowledge, this is the first report on the characteristics of long-term survivors of AGC treated with SP, although there have been a few reports of long-term survivors of AGC treated with palliative chemotherapy [11, 12]. Yoshida et al. [12] reported that 11 of 497 (2 %) patients achieved 5-year survival in four phase II trials and one phase III trial conducted by JCOG. All patients had good PS (0 or 1), and 10 of 11 (91 %) had only one metastatic site: 8 (73 %) involving the abdominal lymph nodes and 2 (18 %) involving the liver. A recent study by Hosokawa et al. [11] reported that 9 of 92 (10 %) patients who had received S-1 monotherapy survived for more than 3 years. All 9 patients had a PS of 0 or 1, and 8 (89 %) had only one metastatic site: 6 (67 %) involving the peritoneum and 2 (22 %) involving the abdominal lymph nodes. In our study, 12 of 104 (12 %) patients with a follow-up period of at least 3 years survived for more than 3 years. Similar to previous studies, all 12 patients had good PS (0 or 1) and 8 (67 %) had only one site of metastasis, including the peritoneum in 2, abdominal lymph nodes in 3, liver in 2, and lung in 1 patient. Interestingly, 4 of 7 (57 %) patients who were alive during the follow-up period were classified into the good-risk group and had prior gastrectomy.

In conclusion, we identified three prognostic OS factors in AGC patients receiving SP as first-line chemotherapy in a clinical setting. A simple prognostic index was developed with different OS rates among the three risk groups. In AGC patients with good PS, the involvement of only one metastatic site increased the patient's probability of achieving long-term survival.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Jemal A, Bray F, Center MM et al (2011) Global cancer statistics. CA Cancer J Clin 61:69–90
2. Glimelius B, Ekstrom K, Hoffman K et al (1997) Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol 8:163–168
3. Murad AM, Santiago FF, Petroianu A et al (1993) Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer (Phila) 72:37–41
4. Pyrhonen S, Kuitunen T, Nyandoto P et al (1995) Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. Br J Cancer 71:587–591
5. Ajani JA, Moiseyenko VM, Tjulandin S et al (2007) Clinical benefit with docetaxel plus fluorouracil and cisplatin compared with cisplatin and fluorouracil in a phase III trial of advanced gastric or gastroesophageal cancer adenocarcinoma: the V-325 Study Group. J Clin Oncol 25:3205–3209
6. Cunningham D, Starling N, Rao S et al (2008) Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 358:36–46
7. Koizumi W, Narahara H, Hara T et al (2008) S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 9:215–221
8. Koo DH, Ryu MH, Ryoo BY et al (2012) Three-week combination chemotherapy with S-1 and cisplatin as first-line treatment in patients with advanced gastric cancer: a retrospective study with 159 patients. Gastric Cancer 15:305–312
9. Chau I, Norman AR, Cunningham D et al (2004) Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer–pooled analysis from three multicenter, randomized, controlled trials using individual patient data. J Clin Oncol 22:2395–2403
10. Lee SS, Lee JL, Ryu MH et al (2007) Combination chemotherapy with capecitabine (X) and cisplatin (P) as first line treatment in advanced gastric cancer: experience of 223 patients with prognostic factor analysis. Jpn J Clin Oncol 37:30–37
11. Hosokawa A, Sugiyama T, Ohtsu A et al (2007) Long-term outcomes of patients with metastatic gastric cancer after initial S-1 monotherapy. J Gastroenterol 42:533–538
12. Yoshida M, Ohtsu A, Boku N et al (2004) Long-term survival and prognostic factors in patients with metastatic gastric cancers treated with chemotherapy in the Japan Clinical Oncology Group (JCOG) study. Jpn J Clin Oncol 34:654–659
13. Kim JG, Ryoo BY, Park YH et al (2008) Prognostic factors for survival of patients with advanced gastric cancer treated with cisplatin-based chemotherapy. Cancer Chemother Pharmacol 61:301–307
14. Boku N, Yamamoto S, Fukuda H et al (2009) Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol 10:1063–1069
15. Ajani JA, Rodriguez W, Bodoky G et al (2010) Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol 28:1547–1553
16. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
17. Koo DH, Ryoo BY, Kim HJ et al (2011) A prognostic model in patients who receive chemotherapy for metastatic or recurrent gastric cancer: validation and comparison with previous models. Cancer Chemother Pharmacol 68:913–921

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

*Hansjochen Wilke, Kei Muro, Eric Van Cutsem, Sang-Cheul Oh, Gyorgy Bodoky, Yasuhiro Shimada, Shuichi Hironaka, Naotoshi Sugimoto, Oleg Lipatov, Tae-You Kim, David Cunningham, Philippe Rougier, Yoshito Komatsu, Jaffer Ajani, Michael Emig, Roberto Carlesi, David Ferry†, Kumari Chandrawansa, Jonathan D Schwartz, Atsushi Ohtsu, for the RAINBOW Study Group**

Summary

Background VEGFR-2 has a role in gastric cancer pathogenesis and progression. We assessed whether ramucirumab, a monoclonal antibody VEGFR-2 antagonist, in combination with paclitaxel would increase overall survival in patients previously treated for advanced gastric cancer compared with placebo plus paclitaxel.

Methods This randomised, placebo-controlled, double-blind, phase 3 trial was done at 170 centres in 27 countries in North and South America, Europe, Asia, and Australia. Patients aged 18 years or older with advanced gastric or gastro-oesophageal junction adenocarcinoma and disease progression on or within 4 months after first-line chemotherapy (platinum plus fluoropyrimidine with or without an anthracycline) were randomly assigned with a centralised interactive voice or web-response system in a 1:1 ratio to receive ramucirumab 8 mg/kg or placebo intravenously on days 1 and 15, plus paclitaxel 80 mg/m² intravenously on days 1, 8, and 15 of a 28-day cycle. A permuted block randomisation, stratified by geographic region, time to progression on first-line therapy, and disease measurability, was used. The primary endpoint was overall survival. Efficacy analysis was by intention to treat, and safety analysis included all patients who received at least one treatment with study drug. This trial is registered with ClinicalTrials.gov, number NCT01170663, and has been completed; patients who are still receiving treatment are in the extension phase.

Findings Between Dec 23, 2010, and Sept 23, 2012, 665 patients were randomly assigned to treatment—330 to ramucirumab plus paclitaxel and 335 to placebo plus paclitaxel. Overall survival was significantly longer in the ramucirumab plus paclitaxel group than in the placebo plus paclitaxel group (median 9·6 months [95% CI 8·5–10·8] *vs* 7·4 months [95% CI 6·3–8·4], hazard ratio 0·807 [95% CI 0·678–0·962]; p=0·017). Grade 3 or higher adverse events that occurred in more than 5% of patients in the ramucirumab plus paclitaxel group versus placebo plus paclitaxel included neutropenia (133 [41%] of 327 *vs* 62 [19%] of 329), leucopenia (57 [17%] *vs* 22 [7%]), hypertension (46 [14%] *vs* eight [2%]), fatigue (39 [12%] *vs* 18 [5%]), anaemia (30 [9%] *vs* 34 [10%]), and abdominal pain (20 [6%] *vs* 11 [3%]). The incidence of grade 3 or higher febrile neutropenia was low in both groups (ten [3%] *vs* eight [2%]).

Interpretation The combination of ramucirumab with paclitaxel significantly increases overall survival compared with placebo plus paclitaxel, and could be regarded as a new standard second-line treatment for patients with advanced gastric cancer.

Funding Eli Lilly and Company.

Introduction

Gastric cancer is the fifth most common malignancy, and the third leading cause of cancer mortality worldwide.[1] Currently, platinum-based and fluoropyrimidine-based combinations are accepted worldwide as established first-line drug regimens.[2] There are not many treatment options after failure of first-line therapy. In randomised trials, selected second-line chemotherapy significantly improved overall survival compared with best supportive care,[3–5] however, median survival was less than 6 months. Therefore, new, more active second-line treatment options are needed.

VEGF and VEGFR-2-mediated signalling and angiogenesis contribute to the pathogenesis of gastric cancer. In patients with gastric cancer, circulating VEGF levels are associated with increased tumour aggressiveness and reduced survival.[6,7] In animal models of gastric adenocarcinoma, VEGFR-2 inhibition reduced tumour growth and vascularity.[8] First-line treatment with bevacizumab, a VEGF-A-directed monoclonal antibody, in combination with chemotherapy was associated with significantly improved proportions of patients achieving an objective response and progression-free survival, and non-significantly improved overall survival in patients with metastatic gastric cancer.[9,10] Ramucirumab, a human IgG1 monoclonal antibody VEGFR-2 antagonist, prevents ligand binding and receptor-mediated pathway activation in endothelial cells.[11] Paclitaxel was chosen for the

Lancet Oncol 2014

Published Online September 18, 2014 http://dx.doi.org/10.1016/S1470-2045(14)70420-6

See Online Comment http://dx.doi.org/10.1016/S1470-2045(14)70464-4

*Principal investigators from the participating centres are listed in the appendix.

†Now employed at Eli Lilly and Company, Indianapolis, IN, USA

Department of Medical Oncology/Haematology, Kliniken Essen-Mitte, Germany (Prof H Wilke MD); Aichi Cancer Center Hospital, Japan (K Muro MD); University Hospitals Leuven and Katholieke Universiteit Leuven, Leuven, Belgium (Prof E Van Cutsem MD); Korea University Guro Hospital, Seoul, South Korea (Prof S-C Oh MD); St László Hospital, Department of Oncology, Budapest Gastrointestinal Medical Oncology, Budapest, Hungary (Prof G Bodoky MD); National Cancer Center Hospital, Tokyo, Japan (Y Shimada MD); Clinical Trial Promotion Department, Chiba Cancer Center, Japan (S Hironaka MD); Clinical Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan (N Sugimoto MD); Republican Clinical Oncology Dispensary, Ufa, Russia (Prof O Lipatov DSc); Seoul National University Cancer Hospital, Seoul, South Korea (Prof T-Y Kim PhD); Royal Marsden Hospital, London, UK (Prof D Cunningham MD); Centre Hospitalier Universitaire Georges Pompidou Assistance Publique-Hôpitaux de Paris, Université Paris V, France (Prof P Rougier MD); Hokkaido University Hospital Cancer Center, Japan

(Prof Y Komatsu MD); University of Texas M D Anderson Cancer Center, Houston, TX, USA (Prof J Ajani MD); Eli Lilly Deutschland, Bad Hamburg, Germany (M Emig MD); Eli Lilly Italia, Sesto Fiorentino, Italy (R Carlesi MD); New Cross Hospital, Wolverhampton, UK (Prof D Ferry PhD); Eli Lilly and Company, Bridgewater, NJ, USA (K Chandrawansa PhD); Stemline Therapeutics, New York, NY, USA (J D Schwartz MD); and Gastrointestinal, Oncology, National Cancer Center Hospital East, Japan (A Ohtsu MD)

Correspondence to: Prof Hamjochen Wilke, Kliniken Essen-Mitte, Evang Huyssens-Stiftung/Knappschaft, Klinik für Internistische Onkologie/Hamatologie, Zentrum für Palliativmedizin, Henricstr 92 45136 Essen, Germany h.wilke@kliniken-essen-mitte.de

See Online for appendix

combination based on single-agent second-line trials;[12,14] the results of a retrospective analysis in gastric cancer indicated similar efficacy between frequently used second-line drugs (taxanes or irinotecan).[15] Weekly paclitaxel is better tolerated and more efficacious than 3-weekly paclitaxel in metastatic breast cancer.[16] More recently, in a Japanese randomised trial, weekly paclitaxel was associated with a good toxicity profile compared with irinotecan as second-line therapy in patients with gastric cancer.[17]

We assessed the safety and efficacy of ramucirumab plus paclitaxel in patients with advanced gastric or gastro-oesophageal junction adenocarcinoma with disease progression after first-line combination chemotherapy.

Methods

Study design and patients

RAINBOW was a double-blind, placebo-controlled phase 3 trial. Eligibility criteria included age 18 years and older; having metastatic or non-resectable, locally advanced gastric or gastro-oesophageal junction adenocarcinoma; documented objective radiological or clinical disease progression during or within 4 months of the last dose of first-line platinum and fluoropyrimidine doublet with or without anthracycline; an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1; and measureable or non-measurable evaluable disease (defined with Response Evaluation Criteria In Solid Tumors [RECIST], version 1.1).[18] Exclusion criteria included having squamous or undifferentiated gastric cancer; gastrointestinal perforation, fistulae, or any arterial thromboembolic event within 6 months, or any significant gastrointestinal bleeding or any significant venous thromboembolism within 3 months before randomisation; or poorly controlled hypertension. The appendix provides the full inclusion and exclusion criteria.

Each centre's institutional review board or independent ethics committee approved the study. The trial followed the principles of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonisation. All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to ramucirumab plus paclitaxel or placebo plus paclitaxel using a randomisation sequence generated using the permuted blocks method within each stratum by a statistician not involved in the study activities. Randomisation was stratified by geographic region (region 1, Europe, Israel, Australia, and the USA; region 2, Argentina, Brazil, Chile, and Mexico; and region 3, Japan, South Korea, Hong Kong, Singapore, and Taiwan), time to progression after first dose of first-line therapy (<6 months *vs* ≥6 months), and disease measurability (measurable *vs* non-measurable). This sequence was programmed into a centralised interactive voice or web-response system. Study sites enrolled patients by accessing the centralised interactive voice or web-response system. The interactive voice or web-response system then assigned a unique identification number to each patient, and randomly assigned patients to one of the two treatment groups.

Patients, medical staff, study investigators, individuals who handled and analysed the data, and the funder were masked to treatment assignment. Ramucirumab and placebo for infusion were identical in appearance to preserve masking. Unmasking could be done for individual patients only on the request of a study physician in case knowledge of the identity of study drug was important for the treatment of serious adverse events.

Procedures

Patients received either ramucirumab 8 mg/kg (ImClone Systems, Branchburg, NJ, USA) or placebo intravenously on days 1 and 15, plus paclitaxel 80 mg/m² intravenously on days 1, 8, and 15 of a 28-day cycle. Patients received study treatment until disease progression, unacceptable toxicity, or withdrawal of consent. Crossover between treatment groups was not allowed. Criteria for discontinuation of patients from study treatment, and for dose modifications to manage treatment-related toxicities are presented in the appendix. All patients received supportive care if indicated.

CT scans were done every 6 weeks. Safety data were gathered continuously and local laboratory assessments (including haematology, clinical chemistry, coagulation, and urinalysis [appendix]) were done at baseline, before each treatment, at the end of therapy, and 30 days after the last dose of study drug; adverse events were graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 4.02).[19] We planned to assess quality of life every 6 weeks until progression using the European Organisation for Research and Treatment of Cancer quality-of-life questionnaire (EORTC QLQ-C30, version 3.0)[20] and the EuroQoL five-dimension, three-level health status questionnaire (EQ-5D-3L).[21] Performance status was assessed at the start of each cycle, at the end of therapy, and at the 30-day follow-up. Blood for analysis of anti-ramucirumab antibodies (immunogenicity) was obtained at baseline, day 15 of cycle 2 and day 1 of cycle 4, and at the 30-day follow-up, and patients' sera were analysed as detailed in the appendix.

Outcomes

The primary outcome was overall survival, defined as the time from randomisation to death from any cause. Secondary outcomes were progression-free survival, defined as time from randomisation to radiographic progression or death; objective tumour response, defined as the proportion of patients who had a best response of complete response or partial response; disease control, defined as the proportion of patients who had a best

response of complete response, partial response, or stable disease; patient-reported outcomes, as assessed using EORTC QLQ-C30 and EQ-5D-3L; immunogenicity of ramucirumab, where a treatment-emergent antibody-positive response was defined as a post-baseline positive response greater than four times increase in the antibody titre, or a missing baseline assessment and an on-treatment titre of at least 1:20; and safety. Disease progression and tumour response were assessed by investigators in accordance with RECIST 1.1.[18]

Statistical analysis

We calculated that to achieve 90% power to detect an overall difference in survival between the two treatment groups (hazard ratio [HR] 0·75; anticipated median overall survival 7·0 months in the placebo plus paclitaxel group *vs* 9·3 months in the ramucirumab plus paclitaxel group) with a one-sided α of 0·025 (two-sided 0·05), 510 deaths were needed, and 663 patients would need to be randomly assigned. The results presented here are based on a two-sided α of 0·05.

We used a log-rank test, stratified by geographic region, time to progression on first-line therapy, and disease measurability, to assess overall survival and progression-free survival. Estimations of time-to-event curves were generated with the Kaplan-Meier method. The HR was estimated with a stratified Cox proportional hazards model. We did a pre-planned multivariate analysis with a stepwise Cox regression model of predefined baseline characteristics to examine the effect of treatment on overall survival and progression-free survival after adjustment for significant prognostic factors. The proportion of patients achieving an objective response and disease control were compared between treatment groups with the Cochran-Mantel-Haenszel test, with adjustment for the randomisation strata. All analyses were done with SAS (version 9.2).

Efficacy analyses were based on the intention-to-treat population and predefined subgroups. The intention-to-treat population comprised all randomly assigned patients, irrespective of whether the patient received study medication. Safety analyses included all patients who received at least one dose of any study drug.

EORTC QLQ-C30 and EQ-5D data were scored according to developer guidelines and summarised descriptively for the intention-to-treat population.[22,23] The EQ-5D index score was calculated using the algorithm developed to represent UK population preferences for health states.[24]

This trial is registered with ClinicalTrials.gov, number NCT01170663.

Role of the funding source

The study funder provided the study drug and collaborated with investigators on protocol, study design, data gathering, analysis, and interpretation, and writing and preparation of this report. HW prepared the first draft in collaboration with the funder and other coauthors. HW had full access to all patient-level study data and all authors approved the submission for publication.

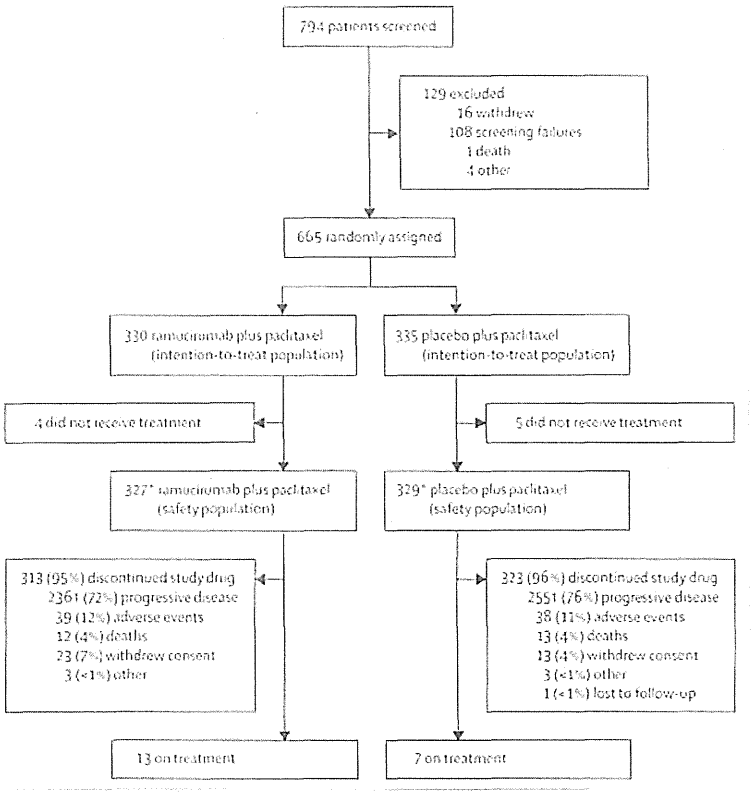

Figure 1: Trial profile

*One patient was randomly assigned to the placebo group, but received one dose of ramucirumab. †Radiographic progression or symptomatic deterioration.

Results

Between Dec 23, 2010, and Sept 23, 2012, 665 (84%) of 794 screened patients were randomly assigned to receive ramucirumab plus paclitaxel (n=330) or placebo plus paclitaxel (n=335) at 170 centres in 27 countries in North and South America, Europe, Asia, and Australia (appendix). Figure 1 shows the trial profile. All patients were included in the efficacy analyses. As of data cutoff (July 12, 2013), with a median follow-up for overall survival of 7·9 months (IQR 4·2–13·0), 516 (78%) of 665 patients had died. 13 (4%) patients in the ramucirumab and paclitaxel group and seven (2%) in the placebo and paclitaxel group are still receiving treatment, and are in the extension phase of the study.

Baseline characteristics of patients and their tumours were generally well balanced between the groups (table 1). 662 of 665 patients received previous treatment with platinum-based and fluoropyrimidine-based chemotherapy regimens, including regimens with an anthracycline (163 [25%]); of the remaining

	Ramucirumab plus paclitaxel (n=330)	Placebo plus paclitaxel (n=335)
Age (years)		
Median (range)	61 (25–83)	61 (24–84)
<65	204 (62%)	212 (63%)
≥65	126 (38%)	123 (37%)
Sex		
Male	229 (69%)	243 (73%)
Ethnic origin*		
White	208 (63%)	199 (59%)
Asian	110 (33%)	121 (36%)
Black or other	12 (4%)	15 (4%)
ECOG performance status		
0	117 (35%)	144 (43%)
1	213 (65%)	191 (57%)
Geographic region†		
1	198 (60%)	200 (60%)
2	23 (7%)	21 (6%)
3	109 (33%)	114 (34%)
Site of primary tumour		
Gastric	264 (80%)	264 (79%)
Gastro-oesophageal junction adenocarcinoma	66 (20%)	71 (21%)
Disease‡		
Measurable	267 (81%)	273 (81%)
Non-measurable	63 (19%)	62 (19%)
Time to progressive disease on first-line therapy‡		
<6 months	250 (76%)	256 (76%)
≥6 months	80 (24%)	79 (24%)
Disease progression		
During first-line therapy	227 (69%)	217 (65%)
Tumor grade		
Well differentiated	28 (8%)	22 (7%)
Moderately differentiated	96 (29%)	106 (32%)
Poorly differentiated	186 (56%)	186 (56%)
Unknown or missing	20 (6%)	21 (6%)
(Continued from previous column)		
Histological subtype (Lauren classification)		
Intestinal	145 (44%)	135 (40%)
Diffuse	115 (35%)	133 (40%)
Mixed	21 (6%)	14 (4%)
Unknown or not available	49 (15%)	53 (16%)
Primary tumour present	209 (63%)	209 (62%)
Number of metastatic sites		
0–2	209 (63%)	232 (69%)
≥3	121 (37%)	103 (31%)
Peritoneal metastases	163 (49%)	152 (45%)
Presence of ascites		
Yes	130 (39%)	107 (32%)
No	200 (61%)	228 (68%)
Weight loss (past 3 months)		
<10%	277 (84%)	286 (85%)
≥10%	53 (16%)	47 (14%)
Previous treatment		
Triplet: platinum and fluoropyrimidine with anthracycline	76 (23%)	87 (26%)
Doublet: platinum and fluoropyrimidine	253 (77%)	246 (73%)
HER2, EGFR, or other	31 (9%)	26 (8%)
Previous surgery for gastric cancer		
Yes	133 (40%)	126 (38%)
Total gastrectomy	52 (16%)	65 (19%)
Partial gastrectomy	80 (24%)	59 (18%)
Other	1 (<1%)	2 (<1%)

Data are number (%) unless otherwise indicated. ECOG=Eastern Cooperative Oncology Group. *By self-report. †Region 1: Europe, Israel, Australia, and the USA; region 2: Argentina, Brazil, Chile, and Mexico; and region 3: Japan, South Korea, Hong Kong, Singapore, and Taiwan. ‡As reported in the interactive voice response system.

Table 1: **Baseline characteristics of patients and their tumours in the intention-to-treat population**

three patients, who had protocol violations, two patients in the placebo plus paclitaxel group had received a platinum-based and fluoropyrimidine-based therapy in the neoadjuvant and adjuvant setting and a fluoropyrimidine-based therapy containing irinotecan and fluorouracil in the first-line setting before enrolling on this study, and one patient in the placebo plus paclitaxel group had received fluoropyrimidine monotherapy in the first-line setting and a fluoropyrimidine and platinum combination in the second-line setting. About two-thirds of the patients had disease progression while still on first-line therapy (table 1). Additionally, a large proportion of patients had other poor prognostic factors including poorly differentiated tumours, disease progression within 6 months after the start of the previous therapy, at least three metastatic sites, presence of primary tumour, peritoneal metastases, or presence of ascites (table 1).

There were 256 deaths in the ramucirumab plus paclitaxel group, and 260 in the placebo plus paclitaxel group (figure 2A). Overall survival with ramucirumab plus paclitaxel was significantly longer than with placebo plus paclitaxel (median 9·6 months [95% CI 8·5–10·8] *vs* 7·4 months [95% CI 6·3–8·4], stratified HR 0·807 [95% CI 0·678–0·962]; p=0·017; figure 2A). 6-month overall survival was 72% (95% CI 66–76) in the ramucirumab plus paclitaxel group, and 57% (95% CI 51–62) in the placebo plus paclitaxel group; 12-month overall survival was 40% (95% CI 35–45) and 30% (95% CI 25–35), respectively (figure 2A).

Overall survival was significantly increased in the ramucirumab plus paclitaxel group compared with the placebo and paclitaxel group (see figure 3 for subgroup analyses).