The Need for a New Fluoropyrimidine in Advanced Gastric Cancer Treatment

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Abstract

Fluoropyrimidines have shown efficacy against a variety of cancers and have evolved into a range of different uses and formulations. These drugs have been tested extensively as monotherapies and as part of numerous different chemotherapy combinations. The efficacy and safety profile of bolus intravenous (IV) 5-fluorouracil (5-FU) has been improved by continuous IV administration. The availability of the first 5-FU oral form in Europe, capecitabine, has added a clear value in terms of convenience for patients, while forcing physicians and nurses to learn how to manage the toxicity profile of this compound. S-1 is a new oral formulation combining a 5-FU prodrug (tegafur) and two targeted modulators of its metabolism (gimeracil and oteracil) preserving the efficacy and improving the safety of the prodrug. S-1 has become the backbone treatment for advanced gastric cancer in Japan since its introduction in 1999. Extensive experience from clinical trials, post-marketing studies and patient registries of over 4,000 patients in Japan show that S-1 has improved measures of survival in advanced gastric cancer and has an acceptable safety profile. S-1 has recently been approved for advanced gastric cancer treatment in Europe. Since 5-FU metabolism differs between Asian and Caucasian populations, the introduction of S-1 in Caucasians has necessitated an entirely new clinical trial programme. Phase I trials indicated different dose levels were necessary in Westerners versus Asians (25 versus 40 mg/m²). In the FLAGS study of over 1,000 patients with advanced gastric cancer (the largest study ever conducted in this indication), S-1 plus cisplatin was demonstrated to be non-inferior in efficacy but superior in safety to 5-FU + cisplatin. Based on these results, S-1 was approved in Europe in March 2011 under the trade name Teysuno®. Further clinical trials are in progress to evaluate S-1 in advanced gastric cancer (AGC) and its use as part of triplet therapies is currently being investigated. This will further define the role of S-1 as a key part of advanced gastric cancer management in Western countries.

Keywords

Fluoropyrimidines, advanced gastric cancer, 5-fluorouracil (5-FU), S-1 (tegafur/gimeracil/oteracil), Caucasian

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The fluoropyrimidine drug 5-fluorouracil (5-FU) was originally patented in the US by Heidelberger and Duschinsky in 1957. Since that time, the use of the drug has been extensively developed and its analogues have played a continuing and pivotal role in cancer treatment. 5-FU was for a long time the only drug administered to gastric cancer patients but it subsequently evolved and underwent multiple manipulations, being administered with other compounds and in new schedules to increase its efficacy and safety.

In current clinical practice, fluoropyrimidines are likely to remain a central part of gastric cancer treatment for the foreseeable future; they are the backbone of most of the treatment regimens used in gastro-intestinal cancers. Efficacy and reduced toxicity are key requirements for oncologists and patients. New fluoropyrimidines in clinical development have considerable advantages over older drugs in terms of efficacy and safety. S-1 is a new formulation that consists of a 5-FU prodrug and two targeted modulators of its metabolism, preserving the efficacy and improving the safety of the prodrug.

Following the recent approval of S-1 for use in Western populations after more than 10 years of extensive experience in Japan, the history of the fluoropyrimidines in advanced gastric cancer will be considered, and evidence supporting the use of S-1 from early phases to more recent clinical studies will be reviewed.

Are all Fluoropyrimidines Equal?

The use of fluoropyrimidines in the treatment of advanced gastric cancer has undergone considerable development. In 1968, IV 5-FU was approved in Europe for the treatment of gastric carcinoma. In 2007, capecitabine became available for the first-line treatment of advanced gastric cancer in combination with a platinum salt. In 2011, S-1 was approved for first-line therapy of advanced gastric cancer in combination with cisplatin.

Table 1: Incidence of Hand-foot Syndrome on Comparative Studies of S-1

Study	Treatment Arms	Incidence of HFS (%) All Grades	Incidence of HFS (%) Grades 3–4
FLAGS (Ajani et al., 2010)[3]	S-1 + cisplatin (n=527)	5.4	0.19
	5-FU + cisplatin (n=526)	2.6	0.39
REAL-2 (Cunningham et al., 2008)[4]	epirubicin + cisplatin + capecitabine (n=250)	45.9	10.3
	epirubicin + oxaliplatin + capecitabine (n=244)	39.3	3.1
	epirubicin + cisplatin + 5-FU (n=263)	29.8	4.3
	epirubicin + oxaliplatin + 5-FU (n=245)	28.9	2.7
ML17032 (Ryu and Kang, 2009)[5]	capecitabine + cisplatin (n=160)	22	3.9
	5-FU + cisplatin (n=156)	4	0
SOX vs CAPOX (Kim et al., 2012)[6]	S-1 + oxaliplatin (n=65)	3.1	0
	capecitabine + oxaliplatin (n=64)	25	1.6

5-FU = 5-fluorouracil; FLAGS = First-Line advanced gastric cancer study; REAL2 = Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer study 2; S-1 = tegafur/gimeracil/oteracil combination (Teysuno™).

Four avenues have been exploited in order to improve the therapeutic index of 5-FU. The first avenue consisted of biochemical modulation with methotrexate, leucovorin and interferon.[1,2] The second avenue involved optimising the dosing schedule. For many years, it has been believed that continuous infusion of 5-FU channels its mechanism of action toward the DNA pathway – the basis of its anti-tumour activity – whereas a bolus dose diverts its activity toward the RNA pathway, which is believed to be the main cause of toxicity. Fifty-six years later, this is not an established fact, merely a supposition. The third avenue involved the development of oral agents for the convenience of clinicians and patients through the development of the 5-FU prodrugs. Finally, the fourth avenue focused on the metabolism of the agent. An increased understanding of each step of the 5-FU metabolism has allowed the selection of modulators targeting key enzymes involved in 5-FU degradation and activation.

Advances in understanding of the mechanism of action of 5-FU have led to the development of strategies that increase its anticancer activity. 5-FU alone is inactive and needs to be activated to the deoxy-nucleotide level, with the formation of 5-fluoro-2′-deoxyuridine 5′-monophosphate (FdUMP), by the action of thymidine phosphorylase (TP). FdUMP blocks thymidylate synthase (TS), the enzyme responsible for the last and crucial step of catalysis in DNA synthesis. 5-FU can also be activated via its conversion to 5-fluorouridine-5′-monophosphate (FUMP), which is incorporated into RNA as a nucleotide analogue that subsequently induces malfunction. Normally, 85 % of 5-FU is catabolised without being activated through its degradation to fluoro-beta-alanine by the enzyme dihydropyrimidine dehydrogenase (DPD). Without this degradation the level of active metabolites will increase substantially, causing intolerable toxicity.

S-1 is the international non-proprietary name (INN) of a fixed combination of three compounds that was selected to enhance 5-FU therapeutic effect while reducing toxicity. The first component is a 5-FU prodrug tegafur that has a sugar moiety attached to the fluorinated base and allows a reproducible high level absorption of 5-FU-based compound in the gastrointestinal (GI) tract. The second component is 5-chloro-2,4-dihydroxypyridine (CDHP or gimeracil), which inhibits dihydropyrimidine dehydrogenase (DPD). The third component is a potassium oxonate (OXO or oteracil) compound that inhibits orotate phosphoribosyl transferase (OPRT) at the start of the pathway of activation to FUMP. S-1 is marketed under different brand names around the world: TS-1® in Japan and Teysuno® in Europe.

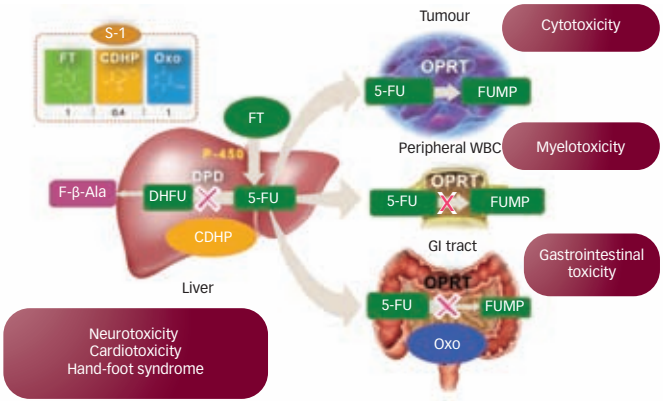
The formulation of S-1 has three possible beneficial consequences. Firstly, in blocking DPD, gimeracil allows a dramatic decrease in the quantity of 5-FU prodrug needed to achieve the active AUC of 5-FU compared with the dose of 1,000 mg/m² bid for capecitabine. In fact, the 25 mg/m² bid dose of tegafur provided by S-1 is 40 fold lower than that of capecitabine, resulting in a comparative dose of metabolised 5-FU of 2.5 %. Additionally, the direct action on DPD decreases the accumulation of fluoro-beta-alanine (Yamada et al., 2003) and the consequent occurrence of hand-foot syndrome (HFS) and other toxicities associated with this 5-FU catabolite. Secondly, oteracil blocks OPRT, leading to a decrease in activation of 5-FU into FUMP, especially in normal tissues, and, therefore, a decrease in gastrointestinal and haematological toxicities. Thirdly, 5-FU can be transformed in the tumour cells in its active form so that it is no longer broken down and is channelled towards FdUMP, triggering a more selective antineoplastic activity. *Figure 1* summarises the mechanism of action of this agent and demonstrates the way in which S-1 interferes and affects the metabolism of 5-FU in a targeted way.

In terms of reducing fluoro-beta-alanine levels by blocking the catabolism of 5-FU, all clinically available fluoropyrimidines can be distinguished into two classes: those that inhibit degradation, known as DPD inhibitory fluoropyrimidines (DIF), including tegafur-uracil, eniluracil and S-1, and those that do not contain a catabolism inhibitor such as IV 5-FU and capecitabine. Essentially, the DIF type of blocking agents substantially reduces fluoro-beta-alanine production and would be expected to reduce toxicity such as the incidence of HFS.

Patients receiving drugs of the DIF category have very low levels of HFS all grades, whereas patients receiving capecitabine show a high incidence of HFS, as do recipients of continuous infusion FU with bolus. When DIF compounds, including S-1, are employed, the incidence of grade 3-4 HFS is reduced to almost zero, as opposed to a 10 % level of severe toxicity with non-DIF compounds. In cancer treatments, theory and preclinical data rarely correspond exactly; but these findings are an example of a correspondence between a postulated mechanism and actual clinical data.

Animal studies involving treatment with a fluoropyrimidine without interference with the RNA-directed pathway, including the activation modulator, resulted in a serious degradation of the intestinal villi and crypts. When oteracil was added however, the anti-RNA effect was blocked and the intestinal villi were protected, as well as the crypts. In a study of 3,800 patients with gastric cancer who were receiving at least fluoropyrimidine plus oteracil treatment and listed in Japanese registry, the incidence of Grade 3–4 diarrhoea was only 2 %.[8] This

Figure 1: The Mechanism of Action of 5-fluorouracil showing the Inhibitory Action of S-1 (Teysuno®)



5-FU = 5-fluorouracil; CDPH = 5-chlorodihydro-pyrimidine; DHFU = 5', 6'- dihydro-5-fluorouracil; DPD = dihydropyrimidine dehydrogenase; FT = 1-(2-tetrahydrofuryl)-5-fluorouracil; FUMP = 5-fluorouridine-5'-monophosphate; OPRT = orotate phosphoribosyl transferase; Oxo = potassium oxonate; WBC = white blood cells. Source: data presented by Y Yamada.

value is consistent with clinical experience but has not been observed in randomised trials. More accurate reporting of the occurrence of diarrhoea in clinical trials conducted in Caucasians is needed to demonstrate the shorter duration and better response to treatment of these symptoms with S-1 than with other 5-FU preparations.

Pharmacokinetic analysis of 5-FU showed that to achieve similar drug exposure, expressed as area under the curve (AUC), in non-Asian patients as in Asian patients, the dose should be reduced. This finding indicates that the metabolism of S-1 is substantially different between Western and Asian populations. As a result of this observation, investigators repeated the entire series of clinical trials that had been carried out in Asian patient populations to adapt the drug to Western populations. Pharmacokinetic studies showed that compared with continuous infusion, the levels of fluoro-beta-alanine obtained with S-1 were approximately five times lower than those obtained with 5-FU. The levels for capecitabine, however, were approximately ten-fold higher.

Several studies have compared S-1 with capecitabine both indirectly and directly. In terms of efficacy, the indirect comparisons in randomised Phase III trials have provided strong evidence to support the use of S-1. The ML17032 study evaluating capecitabine plus cisplatin versus 5-FU plus cisplatin found non-inferiority of the capecitabine + cisplatin regimen.[5] The large (n=1,053) First-line advanced gastric cancer study (FLAGS) evaluating S-1 plus cisplatin versus 5-FU plus cisplatin showed non-inferiority of the S-1 plus cisplatin regimen.[3] From these results it may be concluded that in efficacy terms, capecitabine is roughly equal to IV 5-FU and that S-1 is equal to IV 5-FU. However, it cannot be concluded that S-1 is completely equal to capecitabine. In terms of safety, the FLAGS study found that S-1 had a significantly improved safety profile compared to IV 5-FU and cisplatin.[3]

To obtain meaningful safety comparisons between different cancer treatments, a comparable criterion must be defined. HFS is one of the most frequent adverse events necessitating a dose reduction or treatment interruption for capecitabine. The frequency of this parameter and the ability to monitor it in patients has made it a criterion of choice. Moreover, capecitabine-based regimens have shown an overall incidence of HFS of approximately 50 % and a severe incidence of approximately 10 %, whereas, in the FLAGS study, S-1 showed an incidence of less than 6 % with severe grade incidence of less than 1 % (see *Table 1*).

In addition to the randomised Phase III studies, a Phase II study conducted in South Korea (n=129) compared S-1 + oxaliplatin (SOX) with capecitabine + oxaliplatin (CAPOX) in advanced gastric cancer patients.[6] Both the SOX and CAPOX regimens were equally active and well tolerated. A 25 % incidence of all grades of HFS was observed for CAPOX versus only 3.1 % for SOX. In addition, a 1.6 % incidence of grade 3/4 HFS was seen in the CAPOX group versus 0 % in the SOX group. Grade 3/4 neuropathy, nausea, vomiting and asthenia were also less frequent with SOX.

The occurrence of a relevant adverse event, HFS, in indirect Phase III and direct Phase II comparisons of the different oral 5-FUs raises the following question for oncologists: "What will be your choice in daily practice for the treatment of your patients with advanced gastric cancer?"

S-1 (Teysuno®) – 10 Years of Savoir-faire in Asia

The mortality rate due to gastric cancer in Japan has decreased continuously since the 1960s. Gastric cancer, however, remains the second highest cause of cancer-related death, ranking second for males and third for females in Japan.[9] The five-year survival rates for gastric cancer between 1990 and 1994 at the National Cancer Center Hospital in Japan were not satisfactory at any disease stage, particularly for stage IV for which the rate is less than 10 %.[10]

In the 1960s, the fully active agent 5-FU became available. At the time, drugs were approved by the Japanese Pharmaceutical and Medical Devices Agency (PMDA) according to their response rates, and there was no requirement for Phase III survival benefits data. In the 1990s, irinotecan and taxanes were marketed, as well as S-1, and the survival time was prolonged from 7–8 months to one year. Subsequently, in the 21st century, a more specifically targeted drug, trastuzumab, has been developed for human epidermal growth factor receptor 2 (HER-2)-positive subgroup, constituting the only recent progress in biological therapies in the gastric cancer field.

Data of two late Phase II studies conducted in patients with advanced gastric cancer reported response rate for S-1 monotherapy of 49.0 and 44.2 %, respectively.[11,12] S-1 was very effective at the primary disease site for 39 and 28.9 %, respectively. The frequency of side effects was generally very low. The most commonly observed grade 3/4 toxicities were neutropenia and diarrhoea, with only a 2 % incidence rate. Moreover, the median OS were 250 and 207 days, whereas the one year OS rates were 37 and 36 %, respectively.

In the Japanese Nationwide Post-Marketing Survey of S-1, involving 3,808 Japanese patients, the toxicity profile of S-1 was shown to be similar to that reported in the late Phase II studies. Diarrhoea of grade ≥3 was only 2 %, but the incidence of neutropenia was 6 %. The toxicity of S-1, especially haematological toxicity, was related to creatinine clearance. This was not surprising given that CDHP, which is a DPD inhibitor, is excreted from the kidney. In patients with renal failure, the incidence of haematological toxicities was higher: 40 % (8/20) for a standard initial dose versus 23.5 % (4/17) for a reduced initial dose (for patients with creatinine clearance values <30 mL/min).[8] Therefore, when administering S-1, renal function must be checked and dose adjustments must be made according to age and gender.

Compared with other Japanese Phase II clinical trials of other fluoropyrimidines or cytotoxic agents, S-1 monotherapy was extremely high (see *Table 2*). In the first Japanese Phase III clinical trial conducted by the Japan Clinical Oncologist Group (JCOG) in patients with unresectable advanced/recurrent gastric cancer (JCOG 9205), 5-FU continuous infusion (800 mg/m^2 24 h continuous infusion (CI), D1–5, q4w) was the standard treatment. The test arms were tegafur/uracil (375 mg/m^2 daily) plus mitomycin C (5 mg/m^2 weekly) and 5-FU (800 mg/m^2, 24 h CI, D1-5) plus cisplatin (20 mg/m^2, D1-5, q4w). 5-FU plus cisplatin did not show superiority to 5-FU continuous infusion.[13] Therefore, the control arm with 5-FU continuous infusion (800 mg/m^2 24 h CI, D1–5, q4w) was selected in the next Phase III clinical trial, JCOG 9912. In this study, the test arms were S-1 monotherapy (80, 100 and 120 mg/body/day for body surface area <1.25 m^2, 1.25 - < 1.5 m^2 and ≥ 1.5, respectively, D1-28, q6w) and irinotecan (70 mg/m^2, D1, 15) plus cisplatin (80 mg/m^2, D1, q4w) with a primary endpoint of overall survival (OS). S-1 monotherapy was shown to be non-inferior to 5-FU continuous infusion; the median survival time for S-1 was 11.4 months and the hazard ratio (HR) relative to 5-FU continuous infusion was 0.832 (95 % CI: 0.68–1.01, p=0.0005).[14]

Interestingly, in JCOG 9912 study, the expression of DPD in patients with diffuse type gastric cancer receiving S-1 (poorly differentiated carcinoma, signet-ring cell carcinoma, mucinous adenocarcinoma, n=82) was significantly higher than in patients with intestinal type (papillary or tubular adenocarcinoma, n=86) following the Lauren classification (p<0.001). Hence, 5-FU may not be sufficient for this group of patients. The median progression-free survival (PFS) among 5-FU- or S-1-treated patients with tumours expressing higher levels of DPD was 2.1 and 4.2 months, respectively (HR=2.05; 95 % CI: 1.13–3.71; p=0.016) and S-1 maintained its efficacy in patients with both high and low DPD expression.[15]

The S-1 Plus cisplatin versus S-1 In RCT In the Treatment for Stomach cancer (SPIRITS) study investigated the efficacy of S-1 (80–120 mg/day, D1–21) plus cisplatin (60 mg/m^2, D8, q5w) compared with S-1 monotherapy (80–120 mg/day, D1–28, q6w).[16] This was the first trial to demonstrate the direct survival benefit of S-1 plus cisplatin compared with S-1 monotherapy. S-1 plus cisplatin showed statistically significant survival benefits. The survival rates were 54 % for S-1 in combination with cisplatin versus 47 % for S-1 monotherapy at one year and 24 % for the combination regimen versus 15 % for monotherapy at two years (p=0.04, HR=0.77, 95 % CI; 0.61–0.98).

On the basis of results from these two pivotal trials, S-1 monotherapy appears to be non-inferior to 5-FU. The S-1 plus cisplatin combination however, is superior to S-1 monotherapy. The S-1 plus cisplatin combination regimen has therefore been considered as a standard chemotherapy for unresectable (advanced or metastatic) gastric cancer patients. In the Japanese gastric cancer treatment guidelines 2010,[17] S-1 plus cisplatin is recommended for gastric cancer as a first-line treatment. When S-1 plus cisplatin is considered inappropriate, either S-1 or 5-FU should be delivered as a single agent, depending on the condition of the patients.

In a Phase III trial of gastric cancer, S-1 was compared with S-1 plus irinotecan. Irinotecan was administered at a dose of 80 mg/m^2 on day 1 and day 15, every five weeks.[18] The primary endpoint was also OS. The HR was 0.856 (p=0.233), the median OS were 10.5 months for S-1 alone and 12.8 months for S-1 with irinotecan and the one-year survival rates were 44.9 and 52.0 %, respectively; however, these were not significantly different. In a further trial, S-1 alone was compared with S-1 plus docetaxel in which the primary endpoint was OS. Docetaxel (40 mg/m^2, D1) plus S-1 (80–120 mg/day, D1–14, q4w) were administrated in the patients. The HR was 0.88. As presented during the last ESMO meeting, the follow up of this trial showed a statistically significant improvement of the overall survival in favour of the S-1 + docetaxel regimen (12.5 versus 10.8 months, p=0.0319).[27b] In recent Phase III trials, S-1 monotherapy showed very similar outcomes with median PFS of four months and median OS of 11 months.[16,18,27]

Table 2: The Response Rate of Japanese Phase II Studies in Advanced Gastric Cancer

Agent	Number of Patients	Response Rate (%)
Doxifluridine (Niitani et al., 1985)[19]	140	14.3
Tegafur/uracil (Ota et al., 1988)[20]	188	27.7
S-1 (Sakata et al., 1998)[11]	51	49.0
S-1 (Koizumi et al., 2000)[12]	43	44.2
Epirubicin (Sakata and Yoshida, 1986)[21]	31	16.1
Cisplatin (Ishibiki et al., 1989)[22]	68	19.1
Irinotecan (Futatsuki et al., 1994)[23]	60	23.3
Docetaxel (Taguchi et al., 1998[24] and Mai et al., 1999[25])	66 63	23.7 23.7
Paclitaxel (Yamada et al., 2001)[26]	60	23.3

Source: Data presented by Y Yamada.

In Japan, S-1 plus cisplatin is currently the standard first-line treatment and 70 to 80 % of patients will eventually receive second-line treatment with irinotecan, docetaxel or paclitaxel monotherapy. More than 50 % of these patients will receive chemotherapy that includes paclitaxel.

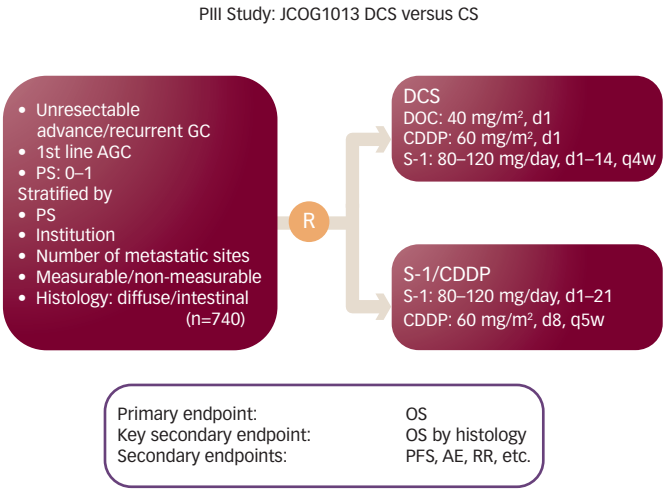
Another promising gastric cancer treatment regimen is S-1 plus oxaliplatin (SOX). In a Phase II study investigating this combination, Oxaliplatin (100 mg/m^2, D1) plus S-1 (80–120 mg/m^2, D1–14, q3w) were administrated in the patients.[28] The response rate was 59 %. The most commonly observed grade 3 or 4 toxicities were neutropenia in 22 % and thrombocytopenia in 13 % of patients. The median OS was 16.5 months. This trial led to an ongoing Phase III trial (n=680) in Japan that is to evaluate non-inferiority of PFS and OS comparing SOX versus S-1 plus cisplatin.

An alternative approach to gastric cancer treatment was evaluated in a Phase I/II trial in which patients received a triplet of docetaxel, cisplatin and S-1 (DCS). Docetaxel (40 mg/m^2) and cisplatin (60 mg/m^2) were given on day 1 of 28-day cycle; S-1 (40 mg/m^2) was given twice daily on days 1–14.[29] The most commonly observed grade 3/4 toxicity was neutropenia in 70 % of patients. The median PFS was 8.7 months and the median OS was 18.5 months. This DCS regimen showed marked efficacy against intestinal and diffuse types of gastric cancer. In this study, down-staging of gastric cancer was achieved in nine (19 %) of 48 patients who responded to DCS.

The DCS is also being compared with a S-1 and cisplatin and combination in another ongoing Phase III trial in patients with unresectable, recurrent or advanced gastric cancer in Japan (JCOG 1013) (see *Figure 2*). The aim of this study is to evaluate superiority of OS (n=740).

For HER2-positive gastric cancer patients, there are currently three Phase II clinical trials with S-1 in progress in Japan and Southeast Asia

Figure 2: Schema of Phase III Trial Comparing the DCS with Cisplatin and S-1 Combination in Patients with Unresectable, Recurrent or Advanced Gastric Cancer in Japan



AE = adverse event; AGC = advanced gastric cancer; CDDP = cisplatin; CS = cisplatin and S-1; DCS = docetaxel, cisplatin and S-1; DOC = docetaxel; GC = gastric cancer; JCOG = Japan Clinical Oncology Group; OS = overall survival; PFS = progression-free survival; PS = performance status; RR = response rate.

(n=25–60). In two of them, a combination of S-1 plus cisplatin plus trastuzumab is being evaluated and in the other S-1 plus trastuzumab is being investigated in elderly patients.

While S-1 plus cisplatin is the current standard regimen for gastric cancer in Japan, SOX and DCS regimens are likely to become more widely used in gastric cancer once Phase III clinical trial results become available in the near future. Phase III data supporting the use of these promising combinations in gastric cancer are now awaited with interest. In clinical use, combination regimens that include S-1 are likely to extend the lives of many patients with advanced gastric cancer.

Established Benefits of S-1 Confirmed in Western Populations

Asian patients, particularly the Japanese, have a markedly different metabolism of anti-cancer drugs compared with Western populations. This phenomenon has been observed with drugs such as 5-FU for which the doses used in Asian patients are much higher than are normally used in Caucasians.

The combination of S-1 and cisplatin is highly active in Japanese patients with advanced gastric cancer. Following the discovery of regional dose variations of one of the S-1 components, it was necessary early in drug development to define the optimal dosing of both S-1 and cisplatin in combination for use in a Caucasian patient population. This necessitated a Phase I pharmacokinetic study in which a combination of S-1 and cisplatin were used to treat advanced gastric carcinoma.[30] In the Japanese population, given an S-1 dose of 32 to 40 mg/m^2, the exposure, as expressed as the AUC, is around 700 ng x h/mL.

In the Caucasian population, to reach a similar AUC with an acceptable tolerability, it is necessary to decrease to a dose of 25 mg/m^2 in combination with cisplatin and it is necessary to decrease to 30 mg/m^2 in monotherapy.[30b]

The design of this Phase I trial allowed various levels of dose escalation, and concluded that the recommended doses were 25 mg/m^2 for S-1 and 75 mg/m^2 for cisplatin. At these doses, the incidence of grade 3/4 toxicities was very low although this was a small Phase I study; 6 patients receiving 25/75 mg/m^2/dose S-1/cisplatin, six receiving 30/60 mg/m^2/dose and three receiving 30/75 mg/m^2. At the highest doses the incidence of grade 3/4 toxicities was greater. These findings led to the initiation of a single-arm Phase II study that investigated the efficacy of the recommended dose based on the Phase I trial: 25 mg/m^2 of S-1 twice daily (BID) for three weeks and cisplatin on day 1 at 75 mg/m^2.[31,32] This treatment improved the time to disease progression to one year; one-year survival rate was 42 % and the two-year survival rate was 21 %. The efficacy data, as reviewed by an independent committee, showed that there was a response rate of 55 % and this was confirmed by time to progression and duration of response. The results of 25 mg/m^2 of S-1 BID plus cisplatin 75 mg/m^2 combination confirmed the efficacy of this treatment.

The S-1/cisplatin combination showed an advantageous tolerability profile in which grade 3/4 neutropenia in 19 % of the patients was the main finding. The remaining toxicities were non-haematologic types. These consisted of fatigue/asthenia (grade 3/4) in 24 %, diarrhoea (grade 3 /4) in 13 %, a low incidence of stomatitis, and a low incidence of febrile neutropenia. This is considered to be an acceptable toxicity profile.

The findings of this study led to the FLAGS study, a multi-centre, international Phase III trial focussing on a Caucasian population with advanced metastatic gastric cancer.[3] This study used the recommended doses that were identified in the Phase I study and confirmed in the Phase II: S-1 at 25 mg/m^2 orally BID for three weeks, with one week of rest plus cisplatin at 75 mg/m^2. This was compared with the conventional 5-FU/cisplatin regimen in which 5-FU was given at 1,000 mg/m^2/day over five days and cisplatin was given at a dose of 100 mg/m^2 on day 1 every four weeks. A total of 1,053 patients were randomised and the patient population was stratified according to the extent of disease, prior adjuvant chemotherapy and measurable versus non-measurable disease; the primary endpoint was overall survival. The statistical analysis plan aimed to demonstrate improvement in median survival from 8.5 months in the cisplatin/5-FU arm to 10.5 months in the experimental arm of cisplatin S-1, corresponding to a HR of 0.81. There was also a delayed endpoint of non-inferiority on OS for which the upper limit was 1.10 to reach statistical significance and to retain potentially 74 % of the effect of cisplatin/5-FU. In parallel, the secondary endpoints of the FLAGS study were PFS, safety, time to treatment failure (TTF), response rate, duration of response, time to tumour response, time to tumour progression, clinical benefit and the quality of life using the FACT gastric scale. The patient population was well balanced in both arms. The majority of patients were male and importantly, 86 % were Caucasian.

The cancers were primarily of the stomach, a few subjects had gastro-oesophageal junction disease, and the diffuse histological type was slightly more frequently than the non-diffuse type. Metastatic disease was present in almost all the patients with two-thirds of the patients having more than two metastatic sites and most were measurable. Very few patients had received prior adjuvant chemotherapy and approximately one-third had prior stomach resection.

There was no major difference in treatment compliance between the two arms and the median number of cycles per patient was four, ranging from one to 28 or one to 24. The dose intensities of S-1 and

5-FU were similar (92 and 95 %, respectively). The duration of treatment was also similar to the planned regimen in both arms.

Toxic death under treatment was three times higher in the cisplatin/5-FU arm as compared with S-1/cisplatin. For OS, the first primary objective of superiority was not met (HR= 0.92, *Figure 3*). However, the calculated level of OS non-inferiority was met and showed that S-1/cisplatin is non-inferior to 5-FU/cisplatin (p=0.0068). For the secondary endpoints, PFS was not superior (HR=0.99) but TTF was (HR=0.87, p=0.032) (see *Figure 3*). The Forest plot in Figure 4 shows that no patient subgroups clearly benefited from either treatment regimen. There are slight advantages for both S-1 and 5-FU but no overall trend towards either treatment for any subgroup. There were similar overall response rates for S-1/cisplatin and 5-FU/cisplatin of 29.1 and 31.9 %, respectively. The duration of response was slightly longer for S-1/cisplatin compared with 5-FU/cisplatin.

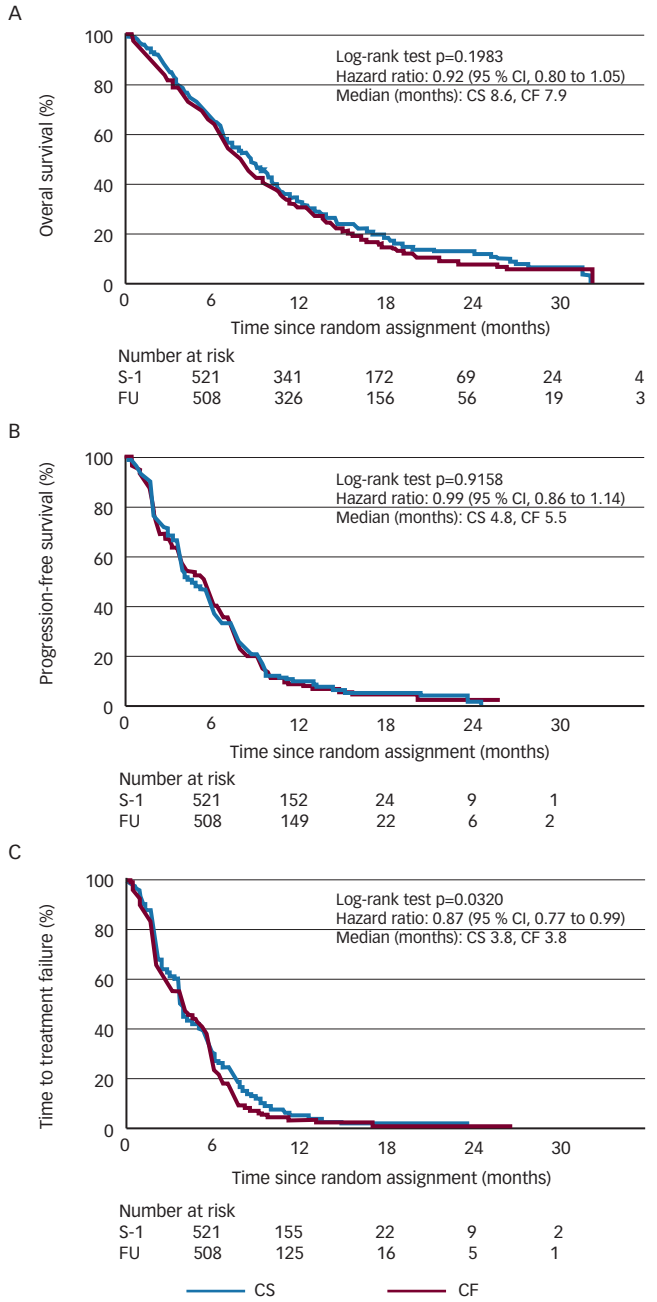
The incidence of severe neutropenia was significantly different between the two treatment groups: approximately 35 % for S-1/cisplatin compared with almost 70 % for 5-FU/cisplatin. There was also a clear advantage in terms of myelosuppression, reflected in a significant reduction of thrombocytopenia and a lower incidence of febrile neutropenia in patients receiving S-1/cisplatin. These results therefore clearly confirm the low myelotoxicity profile of S-1 that was observed in the initial Phase I trial.

In terms of non-haematological toxicity, there was a significant difference in the incidences of diarrhoea (all grades) and the use of anti-diarrhoeal medication was significantly reduced in the cisplatin/S-1 arm compared with the 5-FU/cisplatin arm. There was also a reduction in the incidence of dehydration which is quite often associated with diarrhoea and interestingly, a very low incidence of stomatitis, mucosal inflammation (mostly conjunctivitis), hypophosphatemia and hypomagnesemia with S-1/cisplatin compared with the 5-FU/cisplatin. Therefore the tolerance profile of cisplatin/S-1 appears to be significantly better than that of 5-FU/cisplatin.

In the FLAGS study, renal toxicity appeared to be reduced in the S-1/cisplatin arm compared with 5-FU/cisplatin. The lower dose of cisplatin used in the S-1 arm (75 mg/m^2) versus the IV 5-FU arm (100 mg/m^2) seems to be the main driver of this advantage. Liver function tests showed slight increases in bilirubin as well as all grades of liver-related adverse events for S-1/cisplatin compared with cisplatin/5-FU. Liver impairment showed no statistical difference between treatments and most of this was not associated with symptoms. Thus there was a significantly reduced incidence of serious adverse events with S-1/cisplatin compared with 5-FU/cisplatin. Death related to treatment was significantly reduced by half with S-1/cisplatin. S-1/cisplatin therefore clearly has a superior tolerability profile than 5-FU/cisplatin but with similar efficacy.

It has been observed in previous studies and in general clinical experience that patients prefer oral fluoropyrimidine to the IV form, mostly as a result of improved quality of life. In the FLAGS study, three quality of life parameters were significantly improved in the S-1/cisplatin group.[3] These included the time to more than 5 % weight loss and the physical well being subscale within the FACT Gastric Scale. In addition, the use of anti-diarrhoeal medication was significantly reduced by 40 % with S-1/cisplatin and the use of colony stimulating factors which are associated with neutropenia was reduced by 49 %. S-1/cisplatin therefore clearly provides advantages in terms of quality of life, the need for supportive care, anti-diarrhoeal drugs and colony stimulating factor.[33,33b]

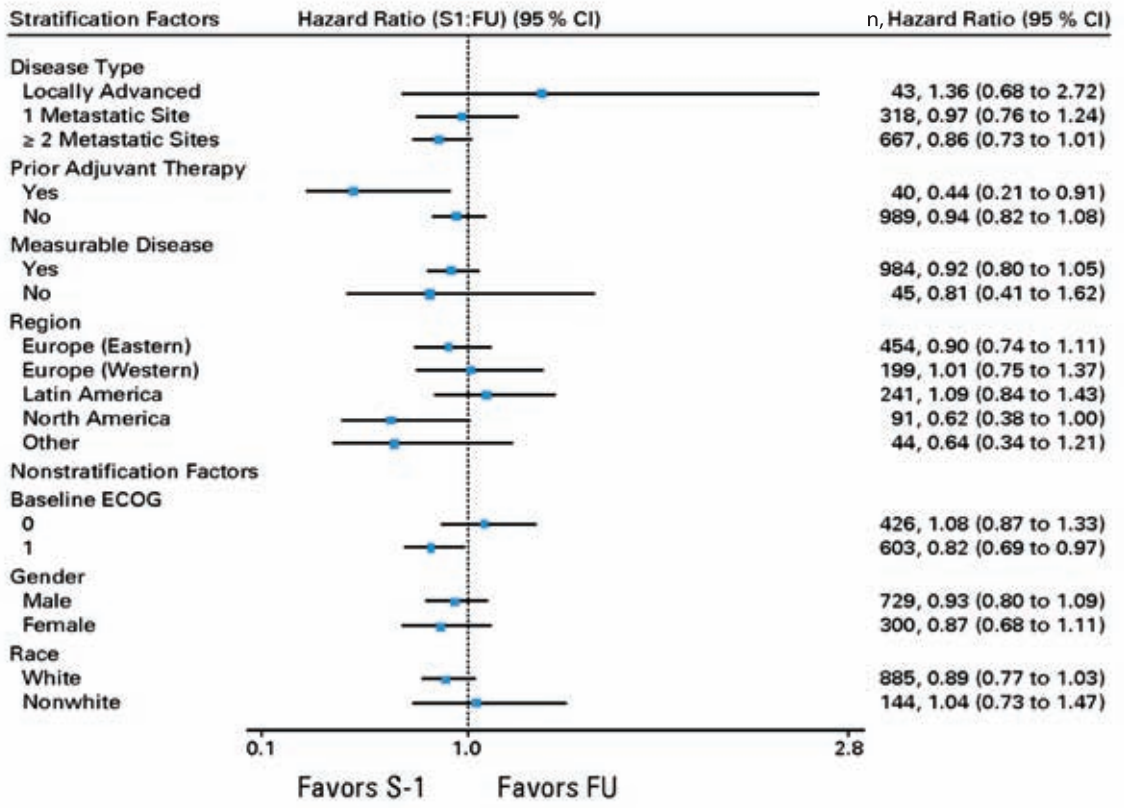
Figure 3: Kaplan-Meier Plot of Overall Survival by the Two Treatment Arms in the FLAGS Study



A: Overall survival; B: progression-free survival; C: time without treatment failure. CF = cisplatin/5-FU; CS =cisplatin/S-1; FU = 5-fluorouracil; S-1 = tegafur/gimeracil/oteracil combination (Teysuno®). Source: Ajani et al., 2010.[3]

The number of hospitalisations also differed between the treatment groups in the FLAGS study. Patients receiving oral drug treatments spent fewer days in hospital and needed to attend only to receive cisplatin. This is reflected in the number of patients that needed to be hospitalised to receive the S-1/cisplatin combination (67.4 %) compared with those receiving 5-FU/cisplatin (80.7 %). Overall, the median number of days patients were hospitalised was twice as high in the 5-FU/cisplatin group (24 days) compared with S-1/cisplatin, (11 days).

Figure 4: Forest Plot of Pre-planned Stratification Factors for Overall Survival in the FLAGS Study



ECOG = Eastern Cooperative Oncology Group; FU = 5-fluorouracil; S-1 = tegafur/gimeracil/oteracil combination (Teysuno®). Source: Ajani et al 2010.[3]

In summary, in the FLAGS study, the primary endpoint of superiority in OS was not met, but the comparison of the non-inferiority calculated level of the upper HR limit 1.10 is highly statistically significant when compared with the upper HR limit obtained in FlAGS for OS 1.05 (p=0.0068).[33]

This approach was considered by the Committee for Medicinal Products for Human Use (CHMP) of the European Medical Agency (EMA), who concluded that the benefits of S-1 are greater than its risk and recommended that it be given marketing authorisation in March 2011. Approval was therefore granted for S-1 for the treatment of advanced unresectable metastatic gastric cancer in combination with cisplatin.

Committed to Filling Knowledge Gaps – The S-1 Development Programme

The FLAGS study provided evidence to support the view that S-1 should be incorporated into treatment strategies for gastrointestinal cancers in Europe. Following an EMA Market Authorisation, S-1 is currently registered as Teysuno® and is already available in Northern European countries including, Denmark, Finland, Norway, Sweden and the UK. It became available in Austria and Germany on the July 1 2012 and other European countries will follow soon.

The projected next step in S-1 development in the US will be the Diffuse Gastric and Esophagogastric Junction Cancer S-1 Trial (DIGEST, NCT 01285557), which uses a similar strategy as the FLAGS study but will look into the superiority of OS for S-1/cisplatin in patients with diffuse type histology. Approximately 60 % of patients in the FLAGS study had the diffuse type of cancers and OS in this group was reported to be better than in those with non-diffuse histology, especially in individuals with lower weight loss. The OS in patients with this histology was 9.0 months for S-1/cisplatin compared with 7.1 months for FU/cisplatin.[34] The trial is being conducted in numerous treatment centres across 20 countries worldwide and plans to recruit at total of 500 patients between 2010 and 2013 with a one-year follow-up.

S-1 may also be used as part of a triplet treatment regimen for gastric cancer but at present there are no data available for Caucasian populations. It remains controversial whether a triplet regimen is needed. However, a meta-analysis demonstrated significant benefit from adding an anthracycline to a platinum and fluoropyrimidine doublet, and ECF (epirubicin plus cisplatin plus protracted infusion 5-FU) is among the most active and well-tolerated regimens.

Docetaxel increases the activity of 5-FU/cisplatin, but is also more toxic when used in a three-weekly regimen, with 29 % complicated neutropenia reported.[35] A randomised Phase II study demonstrated maintained activity with reduced toxicity when a weekly docetaxel schedule was employed in combination with cisplatin and infused 5-FU or capecitabine.[36]

The substitution of capecitabine (X) for 5-fluorouracil (F) and oxaliplatin (O) for cisplatin (C), in the ECF regimen was examined in the recent UK National Cancer Research Institute (NCRI) Randomised ECF for Advanced and Locally Advanced Esophagogastric Cancer 2 (REAL-2) trial, which demonstrated non-inferiority between ECF, ECX, EOF and EOX. The EOX regimen was associated with a longer OS (11.2 versus 9.9 months, HR 0.80, 95 % CI 0.66–0.97; p=0.02) than the reference ECF regimen and the rate of thromboembolism was also significantly reduced by the oxaliplatin substitution (7.6 % compared with 15.1 %, p=0.0003).[37]

These data prompted a Phase I study to evaluate an epirubicin/oxaliplatin/S-1 (EOS) combination. To date, this has recruited eight patients and aims to determine the maximum tolerated dose of S-1, either 20 mg/m^2 (dose level 1) or 25 mg/m^2 (dose level 2) combined with epirubicin at 50 mg/m^2 and oxaliplatin at 130 mg/m^2. This trial will allow a recommended dose of S-1 in an EOS regimen to be established and it will be possible therefore to analyse this EOS regimen in a later Phase III trial and compare it directly with EOX.

A recent study combined S-1 with oxaliplatin in a Caucasian population with advanced solid tumours.[38] In this study, patients received one of two treatment schedules. Schedule A consisted of S-1 25 mg/m^2 BID for 14 consecutive days then a seven-day recovery period in a 21-day cycle and bevacizumab 7.5 mg/kg IV on day 1 of each three-week cycle and oxaliplatin 130 mg/m^2 IV on day 1 of each three-week cycle. Schedule B consisted of S-1 35 mg/m^2 BID on day 1 for seven consecutive days then a seven-day recovery period in a 14-day cycle and bevacizumab 5 mg/kg IV on day 1 of each two-week cycle and oxaliplatin 85 mg/m^2 IV on day 1 of each two-week cycle. The toxicity data show that higher dosages of oxaliplatin also increase grade 1 and 2 peripheral sensory neuropathy. From this trial, therefore, it can be concluded that S-1 and oxaliplatin can be administered with the biological bevacizumab and perhaps other biologics, with acceptable safety and tolerability without evidence of pharmacokinetic interactions.

In another randomised trial conducted in Asia, SOX was compared with CAPOX in the treatment of gastric cancer.[6] Both the SOX and CAPOX regimens were equally active and well tolerated in advanced gastric cancer patients. Grades 3/4 neuropathy, nausea, vomiting and asthenia were less frequent with SOX and as anticipated, HFS at any grade was more frequent for CAPOX (SOX = 3 %; CAPOX = 25 %, p=0.001). Therefore two viable treatments may reduce the risk of HFS. One is the cisplatin/S-1 regimen in a four-weekly regimen and the other is the SOX regimen which is the 130 mg/m^2 oxaliplatin with 25 mg/m^2 S-1 BID regimen in a three-weekly cycle.

Finally, S-1 is also being developed for use in colorectal cancer and ongoing studies in Asia are comparing SOX with other combinations such as folinic acid/fluorouracil/oxaliplatin (FOLFOX).

Conclusion

The 13 years of clinical experience of S-1 in advanced gastric cancer in Japan has shown that the use of this new oral formulation of FU in combination therapy consistently improves survival whilst reducing toxicities and improving tolerability. Non-haematological and haematological adverse events such as diarrhoea and neutropenia are substantially reduced with S-1 compared with other treatments. Pharmacokinetic studies in Western populations showed a marked contrast in the metabolism of S-1 between Japanese and Caucasian populations necessitating substantial dose reductions in Europe to achieve the same AUC values as seen in Japan. This emphasises the importance of independent development programmes for chemotherapy in both Asian and Caucasian patients.

The FLAGS study demonstrated non-inferiority of the S-1 combination versus the 5-FU combination for OS. However, the most important finding from this study was the superior safety profile of the S-1 treatment, making S-1 a suitable replacement for 5-FU in gastric cancer treatment. The results of the DIGEST and other studies are awaited with interest and will help define whether S-1 is suitable for the treatment of more diffuse type tumours and whether it is appropriate as part of a triplet regimen. S-1 has also been investigated in the treatment of solid tumours and in combination with oxaliplatin in which it also shows advantageous safety performance compared with capecitabine regimens. It is therefore likely that fluoropyrimidine-containing combinations, and especially S-1-containing treatments, will continue to be used in gastric cancer treatment for the foreseeable future. ■

1. Grem JL, Chu E, Boarman D, et al., Biochemical modulation of fluorouracil with leucovorin and interferon: preclinical and clinical investigations, *Semin Oncol*, 1992;19:36–44.
2. Perez JE, Lacava JA, Dominguez ME, et al., Biochemical modulation of 5-fluorouracil by methotrexate in patients with advanced gastric carcinoma, *Am J Clin Oncol*, 1998;21:452–7.
3. Ajani JA, Rodriguez W, Bodoky G, et al., 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*, 2010;28:1547–53.
4. Cunningham D, Starling N, Rao S, et al., Capecitabine and oxaliplatin for advanced esophagogastric cancer, *N Engl J Med*, 2008;358:36–46.
5. Ryu MH, Kang YK, ML17032 trial: capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in advanced gastric cancer, *Expert Rev Anticancer Ther*, 2009;9:1745–51.
6. Kim GM, Jeung HC, Rha SY, et al., A randomized phase II trial of S-1-oxaliplatin versus capecitabine-oxaliplatin in advanced gastric cancer, *Eur J Cancer*, 2012;48:518–26.
7. Yamada Y, Hamaguchi T, Goto M, et al., Plasma concentrations of 5-fluorouracil and F-beta-alanine following oral administration of S-1, a dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine, as compared with protracted venous infusion of 5-fluorouracil, *Br J Cancer*, 2003;89:816–20.
8. Nagashima F, Ohtsu A, Yoshida S, et al., Japanese nationwide post-marketing survey of S-1 in patients with advanced gastric cancer, *Gastric Cancer*, 2005;8:6–11.
9. National Cancer Center, Cancer mortality from Vital Statistics in Japan (1958-2010). Vital Statistics in Japan, tabulated by Center for Cancer Control and Information Services, National Cancer Center, Japan, 2011.
10. The Research Group for Population-based Cancer Registration in Japan, Annual reports 1997–2003, 1998–2004. Osaka: Research Group for Population-based Cancer Registration, 2004; and Inoue M, Tsugane S, Epidemiology of gastric cancer in Japan, *Postgrad Med J*, 2005;81:419–24.
11. Sakata Y, Ohtsu A, Horikoshi N, et al., Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) in advanced gastric cancer patients, *Eur J Cancer*, 1998;34:1715–20.
12. Koizumi W, Kurihara M, Nakano S, et al., Phase II Study of S-1, a Novel Oral Derivative of 5-Fluorouracil, in Advanced Gastric Cancer, *Oncology*, 2000;58:191–7.
13. 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.
14. 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.
15. Yamada Y, Yamamoto S, Ohtsu A, Impact of dihydropyrimidine dehydrogenase status of biopsy specimens on efficacy of irinotecan plus cisplatin, S-1, or 5-FU as first-line treatment of advanced gastric cancer patients in JCOG9912, *J Clin Oncol*, 2009;27:15s (abstr 4535).
16. 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.
17. Japanese Gastric Cancer Association, Japanese gastric cancer treatment guidelines 2010 (ver. 3), *Gastric Cancer*, 2011;14:113–23.
18. 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.
19. Niitani H, Kimura K, Sato T, et al., Phase II study of 5'-deoxy-5-fluorouridine (5'-DFUR) in patients with malignant cancer - a multi-institutional cooperative study, *Jpn J Cancer Chemother*, 1985;12:2044–51.
20. Ota K, Taguchi T, Kimura K, Report on nationwide pooled data and cohort investigation in UFT phase II study, *Cancer Chemother Pharmacol*, 1988;22:333–8.
21. Sakata Y, Yoshida Y, Phase II study of epirubicin inoperable or recurrent gastric cancer, *Gan To Kagaku Ryoho*, 1986;13:1887–92.
22. Ishibiki K, Kumai K, Kodaira S, et al., [Phase II study with cisplatin in advanced stomach and colon carcinoma. Cooperative Study Group of Cisplatin for Stomach and Colon Carcinoma], *Jpn J Cancer Chemother*, 1989;16:3185–93.
23. Futatsuki K, Wakui A, Nakao I, et al., [Late phase II study of irinotecan hydrochloride (CPT-11) in advanced gastric cancer. CPT-11 Gastrointestinal Cancer Study Group], *Jpn J Cancer Chemother*, 1994;21:1033–8.
24. Taguchi T, Sakata Y, Kanamaru R, et al., Late phase II clinical study of RP56976 (docetaxel) in patients with advanced/recurrent gastric cancer: a Japanese Cooperative Study Group trial (group A), *Gan To Kagaku Ryoho*, 1998;25:1915–24.
25. Mai M, Sakata Y, Kanamaru R, et al., A late phase II clinical study of RP56976 (docetaxel) in patients with advanced or recurrent gastric cancer: a cooperative study group trial (group B), *Gan To Kagaku Ryoho*, 1999;26:487–96.
26. 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.
27. Kim YH, Koizumi W, Lee KH, et al., Randomized phase III study of S-1 alone versus S-1 plus Docetaxel in the treatment for advanced gastric cancer: The START trial, *J Clin Oncol*, 2011;29(suppl. 4):abstract 7.

27b. Yoshida K Fujii M, Koizumi W, et al., S-1 plus Docetaxel versus S-1 for Advanced Gastric Cancer (START trial) Update 2012, *Ann Oncol*, 2012;23(S9):(abstr LBA19).

28. Koizumi W, Takiuchi H, Yamada Y, et al., Phase II study of oxaliplatin plus S-1 as first-line treatment for advanced gastric cancer (G-SOX study), *Ann Oncol*, 2010;21:1001–5.

29. Koizumi W, Nakayama N, Tanabe S, et al., A multicenter phase II study of combined chemotherapy with docetaxel, cisplatin, and S-1 in patients with unresectable or recurrent gastric cancer (KDOG 0601), *Cancer Chemother Pharmacol*, 2012;69:407–13.
30. Ajani JA, Faust J, Ikeda K, et al., Phase I pharmacokinetic study of S-1 plus cisplatin in patients with advanced gastric carcinoma, *J Clin Oncol*, 2005;23:6957–65.

30b. Hoff PM, Saad ED, Ajani JA, et al., Phase I study with pharmacokinetics of S-1 on an oral daily schedule for 28 days in patients with solid tumors, *Clin Cancer Res,* 2003;9(1):134–42.

31. Ajani JA, Lee FC, Singh DA, et al., Multicenter phase II trial of S-1 plus cisplatin in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma, *J Clin Oncol*, 2006;24:663–7.
32. Lenz HJ, Lee FC, Haller DG, et al., Extended safety and efficacy data on S-1 plus cisplatin in patients with untreated, advanced gastric carcinoma in a multicenter phase II study, *Cancer*, 2007;109:33–40.
33. Ajani JA, Pantigoso WR, Bodoky G, et al., Non inferiority analysis of multicenter phase III comparing Cisplatin/S-1 (CS) with Cisplatin/5-FU (CF) as first-line therapy in patients with advanced gastric cancer (FLAGS): Methodology and Results, *Ann Oncol*, 2012;23:(Suppl. 9):(abstr 668PD).

33b. Bodoky G, Carrato A, Ravaioli A, Ajani JA, Quality of life in FLAGS trial: A randomized, Phase III of Teysuno® (S-1) + cisplatin (CS) compared to 5-FU + cisplatin (CF) in untreated advanced gastric cancer (AGC) patients, *Ann Oncol*, 2012;(S9):(abstr 695P).

34. Ajani JA, Rodriquez W, Bodoky G, et al., Multicenter phase III comparison of cisplatin/S-1 (CS) with cisplatin/5-FU (CF) as first-line therapy in patients with advanced gastric cancer (FLAGS): Secondary and subset analyses, *J Clin Oncol*, 2009;27(suppl. 15) abstract 1145 (ASCO annual meeting, Orlando, Florida, US, 29 Mar – 2 June 2009).
35. Cutsem EV, Moiseyenko VM, Tjulandin S, 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, 2006;24(31):499–7.
36. Tebbutt NC, Cummins MM, Sourjina T, Randomised, non-comparative phase II study of weekly docetaxel with cisplatin and 5-fluorouracil or with capecitabine in oesophagogastric cancer: the AGITG ATTAX trial, *Br J Cancer,* 2010;102(3):475–81.
37. Okines A, Verheij M, Allum W, et al., Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, *Ann Oncol*, 2010;21(Suppl. 5):v50–4.
38. Chung KY, Saito K, Zergebel C, et al., Phase I study of two schedules of oral S-1 in combination with fixed doses of oxaliplatin and bevacizumab in patients with advanced solid tumors, *Oncology,* 2011;81(2):65–72.