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Review

Role of chemotherapy for advanced/recurrent gastric cancer: An individual-patient-data meta-analysis

The GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group [a,b]

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KEYWORDS
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Abstract We conducted an individual-patient-data meta-analysis of the efficacy of chemotherapy on overall survival (OS) and progression-free survival (PFS) in advanced/recurrent gastric cancer (AGC).

Our primary research question was whether the experimental arms of the trials included in the meta-analysis showed a benefit as compared with their corresponding control arms. MEDLINE (up to 2010), Cochrane Central Register of Controlled Trials, National Institutes of Health (NIH) trial registry and proceedings of major oncologic and gastrointestinal cancer meetings were searched. Randomised controlled trials for AGC closed to patient accrual before the end of 2006 were eligible.

As of December 2010, individual patient data were available from 22 trials (4245 patients, representing 47% of the targeted data) of 55 eligible trials. The overall comparison of experimental arms with the corresponding control arms showed statistically significant differences in terms of both OS and PFS. Hazard ratio was 0.88 (95% confidence interval 0.82–0.94, $P < 0.0001$) for OS and 0.81 (0.76–0.88, $P < 0.0001$) for PFS. The results of the sub-analysis of adding a given chemotherapeutic agent to any chemotherapy confirm the results of the overall analysis, with a hazard reduction of 11% for OS ($P < 0.01$) and 26% for PFS ($P < 0.0001$).

This meta-analysis of individual patient data shows that the additions of experimental chemotherapeutic agents to pre-existing control or standard regimens have produced a modest improvement in OS and PFS. Median survival remained below 1 year for all investigated chemotherapy regimens and none emerged as a clear standard.

[a] Membership and addresses of the GASTRIC Group are listed in the Appendix.

[b] Correspondence to: Dr K Oba, Translational Research and Clinical Trial Center, Hokkaido University Hospital, Kita 14, Nishi 5, Kita-ku, Sapporo, Hokkaido 060-8648, Japan; tel.: +81 11 706 7413; e-mail: k.oba@huhp.hokudai.ac.jp

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1. Introduction

Gastric cancer is the second most common cause of cancer mortality worldwide and remains a major global public health problem, although the incidence of gastric cancer has decreased over the three last decades.[1] In the United States (US), as many as 75% of all patients have advanced or metastatic disease at the time of diagnosis, and relative 5-year survival rates for gastric cancer of all stages are about 25%.[2]

After more than 30 years of clinical research the prognosis of advanced/recurrent gastric cancer (AGC) remains grim, with median overall survival (OS) barely exceeding 1 year until recently. Small randomised studies have concluded that combination chemotherapies can significantly prolong median OS compared to best supportive care.[3,4] Several combination chemotherapies have been developed and assessed in randomised studies: FAM (5-fluorouracil (5-FU), doxorubicin and mitomycin C (MMC)),[5] FAMTX (5-FU, doxorubicin, methotrexate),[6] EAP (etoposide, doxorubicin, cisplatin),[7] CF (cisplatin, 5-FU),[8] ELF (etoposide, 5-FU, leucovorin)[4] and ECF (epirubicin, cisplatin, 5-FU) [9,10]; and more recently several combinations with new cytotoxic drugs have been tested, including DCF (docetaxel, cisplatin and 5-FU),[11] IFL (irinotecan, leucovorin, 5-FU),[12] XP (capecitabine, cisplatin)[13,14] and EOX (epirubicin, oxaliplatin and capecitabine).[15] Recent systematic reviews or meta-analyses were either based on published data or focused on specific regimens (eTable 1). In the setting of AGC, however, there are many chemotherapeutic regimens to choose from, but the true benefit of chemotherapy remains unclear, with median OS often less than 1 year together with significant side effects.

GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) is an academic, worldwide project which conducts individual patient-based (IPD) meta-analyses of randomised trials of post-operative adjuvant chemotherapy for resectable gastric cancer, or chemotherapy for AGC.[15] Given the large number of investigated treatments, the absence of well-accepted control, as well as their modest sample sizes and lack of clear results, IPD meta-analysis affords a unique opportunity to cast light on this vexing issue. While waiting for more effective treatments, a better understanding of current results using an IPD meta-analysis should help clarify the overall impact of chemotherapy on AGC.

2. Patients and methods

2.1. Study selection and data extraction

This IPD-based meta-analysis was conducted to determine the efficacy of chemotherapy on OS and progression-free survival (PFS) in AGC. The main inclusion criterion was that the study had to be a randomised controlled trial for AGC that had been closed to patient accrual before the end of 2006. We specified 10 group comparisons among eligible trials, which investigated 5-FU, MMC, anthracyclines, platinum agents, irinotecan and taxanes. Trials investigating immunotherapy, neoadjuvant or adjuvant therapy were excluded. Trials with radiotherapy or intraperitoneal chemotherapy were outside the scope of our research and were excluded.

Data from all published randomised trials comparing chemotherapeutic effects for AGCs were sought electronically. The strategy filter for computerised bibliographic searches of MEDLINE (1970–2010) is described in eTable 2. No restriction on language of publication was considered. The Cochrane Central Register of Controlled trials and the National Institutes of Health (NIH) trial registry (clinicalTrials.gov) and proceedings' books from major oncologic and gastrointestinal cancer meetings were also examined for published results. We also used the search results of the well-conducted review based on aggregate data from Wagner et al.[16,17] To ensure that all relevant trials were included, researchers with expertise in the area were queried for the existence of unpublished trials.

The following data were requested for all individual patients: centre, date of randomisation, date of birth, sex, performance status, disease status at baseline, number of organs involved at study entry, location of metastasis, histology, TNM stage, prior surgery, liver/peritoneum involvement, ascites, date of start of chemotherapy, date of last status, survival status, cause of death, date of progression, progression status, tumour response, date of tumour response and reason for treatment discontinuation. Updated survival status and date of last follow-up were also requested. Data for patients excluded from analysis after randomisation were obtained whenever possible.

2.2. Research questions

The first overall question we investigated was whether the experimental arm or arms of trials included in the meta-analysis showed a benefit compared with the corresponding control arm. To achieve clinical interpretability despite the heterogeneity in treatment regimens tested in the various trials, we defined as 'experimental' the treatment arm which contained the greater number of drugs (e.g. triple combinations versus double combinations, regardless of the drugs involved in the respective regimens). When two arms consisted of regimens containing the same number of drugs, we defined as 'experimental' the treatment arm that included the newer agent, i.e. methotrexate versus MMC, CPT11 versus etoposide, CPT11 versus 5-FU and S-1 versus 5-FU. These conventions allowed us to define a control arm and one or more experimental arms for all trials included in the meta-analysis, except randomised phase II trials that did not

aim to show superiority of the experimental over the control arm. We grouped the different trials according to chemotherapeutic agents. In sub-analysis, we distinguished 'additive comparisons', in which chemotherapy was compared to the same chemotherapy plus an additional agent; 'substitutive comparisons', in which one of the agents in a regimen was substituted by a different agent; and a last category of 'other comparisons'.

Second, we refined the analysis of trials that compared chemotherapy with the same plus an additional compound to investigate classes of agents. This analysis included randomised comparisons of any treatment, including for example best supportive care only versus the same treatment plus a chemotherapeutic agent or combination of agents. Last, we grouped trials that compared any chemotherapy to any other with and without one or more agents of interest, namely 5-FU, MMC, anthracycline, platinum agents, irinotecan or taxane.

2.3. Endpoint

The primary endpoint for this analysis was OS, defined from the date of randomisation to the date of death from any cause. Patients lost to follow-up were censored at the date of last assessment. PFS, defined from the date of randomisation to the date of progression or death from any cause, was also determined. Progression was as assessed by an independent review committee when available, or as reported by the clinician otherwise. Patients lost to follow-up were censored at the patient's last visit date or the last date that the absence of progression was documented. In cases without information on censoring for PFS, the date of last assessment of survival was used as the date of censor. Trials which did not collect information on date of progression were excluded from PFS analyses.

2.4. Data management and quality assessment of the trials

All data were centrally checked with standardised programs. Each trial was reanalysed and compared to the published results. Differences were queried to the corresponding author. In addition to the identification of inconsistencies and missing data, particular attention was paid to the randomisation process and patient follow-up. Randomisation was examined to identify possible differences with a true random process. Balance in the distribution of the main covariates was also investigated. Likewise, distributions of days/months of randomisation were checked to detect anomalies.[18]

2.5. Statistical analysis

Treatment effects on OS and PFS were analysed using a two-sided log rank stratified by study. We used a fixed-effects model and the inverse variance method in which the weight of each trial was proportional to the variance of the number of events. Multi-arm trials suitable for different research questions were analysed in several comparisons. To account for correlation between the different comparisons, the weight of each pair-wise comparison was corrected according to a function of the number of events. For instance, in a three-group trial with d1 and d2 events in the two investigational arms and dc in the control arm, the weight of the two comparisons was modified by a factor equal to $(di + dc/2)/(di + dc)$, with i being equal to 1 or 2. Forest plots of hazard ratios (HR) were produced with one line per trial. Heterogeneity between trials and groups of trials (e.g. defined by different chemotherapy regimens) was tested using chi-squared statistics[19] and measured with the I^2 statistics, which estimates the proportion of variability due to heterogeneity between studies rather than sampling error.[20] All analyses were carried out on all randomised patients according to their allocated treatment arm, irrespective of the received treatment. Patients whose individual survival data were not available were excluded. All analyses were performed with SAS 9.2 using macros from the European Organisation for Research and Treatment of Cancer.

3. Results

Fifty-five eligible studies that had randomised 9054 patients were identified by the end of 2010 (Fig. 1). Data were available from 22 studies, representing 4245 patients (47% of the targeted patients).[4–6,8,12,13,21–36] Demographic and baseline characteristics of all trial data are displayed in Table 1. OS and PFS data were available for 4214 and 4073 patients (20 trials) respectively. No study was excluded due to questionable randomisation. Data were not obtained for 4809 patients in 33 trials because of no reply despite repeated attempts or refusal to share by the principal investigators,[7,9,10,37–53] or because data were lost or inaccessible.[3,54–65] The trials for which data were available were more recent and had better performance status than those with unavailable data (eTable 3). No other differences in baseline characteristics were found.

3.1. Experimental versus control grouped by type of comparison

When all trials included in the meta-analysis were considered for the overall comparison of experimental chemotherapy arms with the corresponding control arms, statistically significant differences were seen with regard to both OS and PFS (Fig. 2 and eFig. 1). HR was 0.88 (95% confidence interval (95%CI) 0.82–0.94, $P < 0.0001$) for OS and 0.81 (95%CI 0.76–0.86, $P < 0.0001$) for PFS. These HRs translated into a median

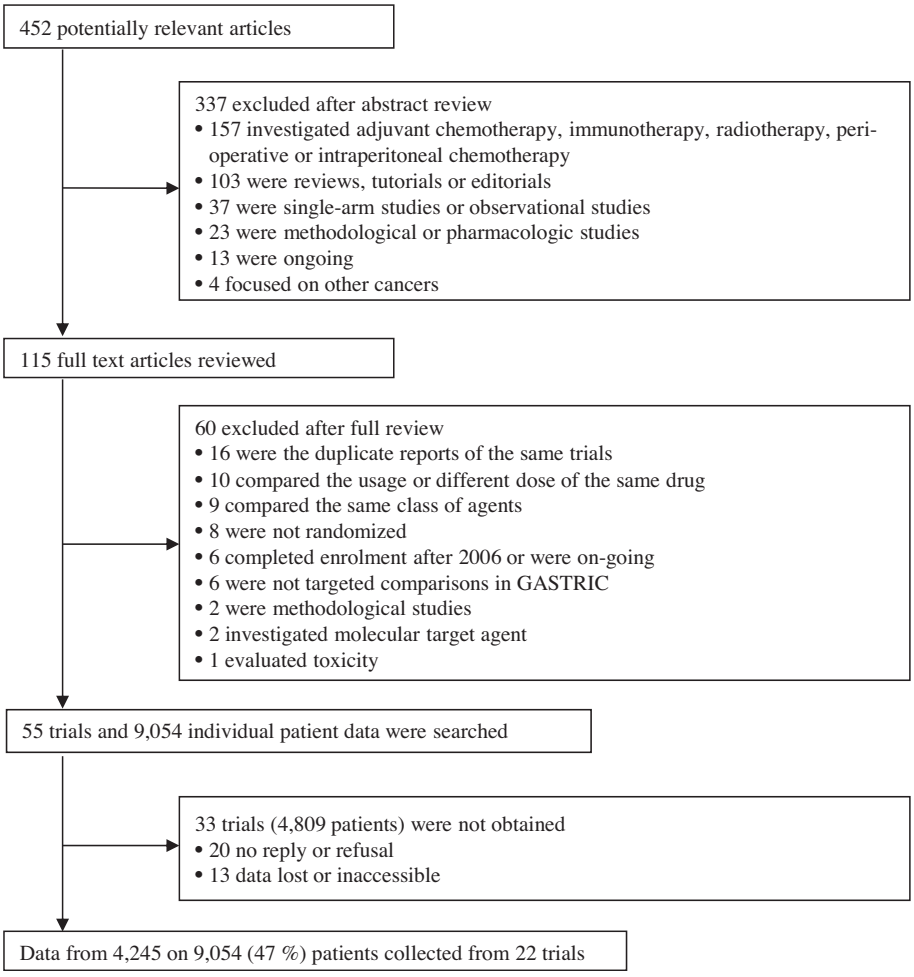

Fig. 1. Study flow chart.

PFS difference of 4 weeks and a median OS difference of 3 weeks (Fig. 3).

No heterogeneity in treatment effect on OS was detected between the three types of comparisons. It was of borderline significance for PFS ($P = 0.04$), with a larger benefit in trials comparing a regimen versus the same regimen plus a new compound. Further, statistically significant heterogeneity was seen among HRs of the various trials for PFS ($P < 0.01$, $I^2 = 44\%$) and to a lesser extent for OS ($P = 0.31$, $I^2 = 11\%$), which was mainly driven by trials from the 'other' type of comparison group. The trials in Fig. 2 and eFig. 1 are ordered according to the date of accrual termination, revealing the absence of any clear trend towards greater benefit in more recent years.

3.2. Any chemotherapy versus the same chemotherapy plus a given chemotherapeutic agent

This analysis also showed a statistically significant difference favouring the addition of a chemotherapeutic agent in terms of PFS in 1786 patients (eFig. 2) and of OS in 1859 patients (eFig. 3). HR was 0.74 (95%CI 0.67–0.81, $P < 0.0001$) for PFS and 0.89 (95%CI 0.80–0.98, $P < 0.01$) for OS. There was no evidence of heterogeneity among HRs of either PFS ($P = 0.18$) or OS ($P = 0.57$).

3.3. Contribution of individual agents

The last set of analyses looked at the randomised comparisons of any treatment regimen not including an agent of interest with the same or a different treatment regimen including the agent. This partially overlaps with the previous analysis. Forrest plots are displayed in eFig. 4 for PFS and eFig. 5 for OS.

For MMC, analysis of 839 patients from 5 trials[5,6,8,21,29] (31% of 2705 targeted patients) showed no difference in terms of PFS (HR = 1.06; 95%CI 0.91–1.24, $P = 0.45$) or OS (HR = 1.15; 95%CI 0.98–1.34, $P = 0.084$). There was, however, substantial heterogeneity between the outcomes of the various trials with regard to both PFS ($P = 0.002$) and OS ($P = 0.003$).

For anthracyclines, analysis of 1320 patients (8 trials[5,21,22,24,26,27,32]) showed no difference with regard to PFS (HR = 0.92; 95%CI 0.82–1.04) or OS

Table 1
List of included trials.

Trial	Chemotherapy schedule		No. of patients		Accrual period	Disease status at entry	Median (range) follow-up days
	Experimental arm	Control arm	Exp	Ctr			
Douglass (1984)[5]	*FAMe*: 5-FU 325 mg/m^2 i.v., days 1 through 5; 5-FU 450 mg/m^2 i.v., day 22; and methyl-CCNU 60 mg/m^2 orally, days 1 and 22; and doxorubicin 40 mg/m^2 i.v., days 1 and 22. Each course was repeated every 6 weeks *FAM*: 5-FU 600 mg/m^2 i.v., days 1, 8, 29, 36; doxorubicin 30 mg/m^2 i.v., days 1 and 29; and mitomycin C (MMC) 10 mg/m^2 i.v., day 1. Courses were repeated every 8 weeks	*FMe*: 5-FU 300 mg/m^2 i.v., days 1 through 5; and methyl-CCNU 175 mg/m^2 orally, day 1. Each course was repeated every 7 weeks	89	48	1977–1981	Not supplied	156 (5–1107)
Cullinan (1985)[21]	*FAM*: 5-FU 600 mg/m^2 i.v., days 1, 8, 29 and 36; doxorubicin 30 mg/m^2, days 1 and 29; and MMC 10 mg/m^2, day 1 *FA*: 5-FU 400 mg/m^2 i.v.; and 40 mg of doxorubicin on day 1 every 4 weeks	*F*: 5-FU 500 mg/m^2 i.v., 5 days first. Courses were repeated at weeks 4 and 8, and every 5 weeks thereafter. [check]	103	53	1977–1980	Regional: 37.7% Metastatic: 62.3%	207 (1–2645)
Wils (1991)[6]	*FAMTX*: 5-FU 1500 mg/m^2 i.v. day 1; methotrexate 1500 mg/m^2 i.v., day 1; leucovorin 15 mg/m^2 orally, every 6 h for 48 h; and doxorubicin 30 mg/m^2 i.v., day 15. Courses were repeated every 4 weeks	*FAM*: 5-FU 600 mg/m^2 i.v. days 1, 8, 29 and 36; doxorubicin 30 mg/m^2 i.v. days 1 and 29; and MMC 10 mg/m^2 i.v. day 1. Courses were repeated every 8 weeks	108	104	1985–1989	Locally adv: 10.9% Metastatic: 68.4% Locally rec: 4.3%	223.5 (1–1406)
Nio (1992)[22]	*CFEpi*: Cisplatin 50 mg/body i.v., day 1; 5-FU 250 mg/body i.v., day 2 through 5; and epirubicin 30 mg/m^2 i.v., day 2. Courses were repeated every 2 weeks	*CF*: Cisplatin 50 mg/body i.v., day 1; and 5-FU 250 mg/body i.v., day 2 through 5. Courses were repeated every 2 weeks	31	27	1989–1991	Locally adv: 15.5% Metastatic: 37.9% Locally rec: 43.1%	82.5 (10–358)
Coombes (1994)[23]	*Epi*: Epirubicin 100 mg/m^2 i.v., day 1. Course was repeated every 3 weeks	*F*: 5-FU 500 mg/m^2 i.v., day 1–5. Course was repeated every 3 weeks	36	33	1985–1988	Loco-regional: 5.8% Peritoneal: 18.8% Metastatic: 69.6%	193.5 (3–1250)
Cullinan (1994)[24]	*FAMe*: 5-FU 325 mg/m^2 i.v., days 1 through 5; 5-FU 450 mg/m^2 i.v., day 22; and doxorubicin 40 mg/m^2 i.v., days 1 and 22. Courses were repeated every 5 weeks. Methyl-CCNU 110 mg/m^2 orally, days 1, repeated every 10 weeks *FAMe plus TZT*: 5-FU 325 mg/m^2 i.v., days 1 through 5; 5-FU 450 mg/m^2 i.v., day 22; doxorubicin 40 mg/m^2 i.v., days 1 and 22; and TZT 250 mg/m^2 i.v., daily for 3 days at 5 weeks. Methyl-CCNU 110 mg/m^2 orally, days 1, repeated every 10 weeks. This full cycle was repeated every 8 weeks *FAC*: 5-FU 300 mg/m^2 i.v., daily for 5 consecutive days; doxorubicin 40 mg/m^2 i.v., on day 1; and cisplatin 60 mg/m^2 i.v., day 1. Courses were repeated every 5 weeks	*F*: 5-FU 500 mg/m^2 i.v., daily for 5 consecutive days. Course was repeated every 5 weeks	184	72	1984–1992	Loco-regional: 43% Metastatic: 57%	198 (2–2048)

(*continued on next page*)

Table 1 (*continued*)

Trial	Chemotherapy schedule		No. of patients		Accrual period	Disease status at entry	Median (range) follow-up days
	Experimental arm	Control arm	Exp	Ctr			
Glimelius (1997)[4]	*ELF*: Leucovorin 350 mg/m^2, etoposide 120 mg/m^2 and 5-FU 500 mg/m^2 daily on 3 consecutive days. Courses were repeated every 3 weeks Or *FL*: 5-FU 500 mg/m^2 i.v. and leucovorin 60 mg/m^2 daily on 2 consecutive days. Courses were repeated every 2 weeks	Best supportive care	30	30	1991–1995	Loco-regional: 70% Metastatic: 30%	206 (6–941)
Yamamura (1998)[25]	*FMTXPira*: methotrexate 50 mg/m^2 i.v.; 5-FU 650 mg/m^2 i.v.; and pirarubicin 20 mg/m^2 i.v. on day 1 and 15. Leucovorin 15 mg/body after 30 h. Courses were repeated every 2 weeks.	*F*: 5-FU 650 mg/m^2 day 1 and 15. Course was repeated every 2 weeks	39	35	1994–1996	Metastatic: 71.6% Locally rec: 28.4%	156.5 (8–882)
Vanhoefer (2000)[26]	*FAMTX*: 5-FU 1500 mg/m^2 i.v. day 1; methotrexate 1500 mg/m^2 i.v. followed after 1 h by 5-FU; leucovorin rescue 30 mg/m^2 was started after 24 h orally every 6 h for 48 h; and doxorubicin 30 mg/m^2 i.v., day 15. Courses were repeated every 4 weeks *ELF*: folinic acid (leucovorin) 300 mg/m^2 i.v.; etoposide 120 mg/m^2; and bolus 5-FU 500 mg/m^2 i.v., for 3 consecutive days. The cycles were repeated every 22 days	*CF*: 5-FU 1 g/m^2 i.v. daily for 5 consecutive days; and cisplatin 100 mg/m^2 i.v., on day 2. The cycles were repeated every 29 days	265	134	1991–1995	Locally adv: 5.0% Metastatic: 16.3% Locally rec: 78.7%	183 (2–2329)
Kim (2001)[27]	*EpiCF*: Epirubicin 50 mg/m^2 i.v. day 1; cisplatin 60 mg/m^2 i.v. day 1; and 5-FU 1000 mg/m^2 i.v., days 1 through 5. The cycles were repeated every 4 weeks	*CF*: 5-FU 1000 mg/m^2 i.v., day 1 through 5; and cisplatin 60 mg/m^2 i.v., day 1. The cycles were repeated every 4 weeks	59	61	1997–2000	Locally adv: 5.0% Metastatic: 95.0%	235 (34–235)
Ohtsu (2003)[8]	*CF*: 5-FU 800 mg/m^2 i.v. day 1 through 5; and cisplatin 20 mg/m^2 i.v., day 1–5. The cycles were repeated every 4 weeks *UFTM*: UFT (uracil/tegafur) 375 mg/m^2 orally, daily; and MMC 5 mg/m^2 i.v., day 1. The cycles were repeated every 4 weeks	*F*: 5-FU 800 mg/m^2 i.v., days 1 through 5. The cycles were repeated every 4 weeks	175	105	1992–1997	Locally adv: 79.3% Metastatic: 20.4%	204 (4–1565)
Pozzo (2004)[28]	*IFL*: Irinotecan 80 mg/m^2 i.v.; and leucovorin 500 mg/m^2 i.v. and 5-FU 2000 mg/m^2 i.v., on days 1, 8, 15, 22, 29 and 36. Cycles were repeated every 7 weeks	*IC*: irinotecan 200 mg/m^2 i.v., day 1; and cisplatin 60 mg/m^2 i.v. day 1. Cycles were repeated every 3 weeks	75	73	1999–2000	Locally adv: 6.1% Metastatic: 90.5% Locally rec: 0.7%	257 (5–664)
Koizumi (2004)[29]	*CMF'*: Cisplatin 70 mg/m^2 i.v., on day 1; MMC 7 mg/m^2 i.v., day 2; and 5'-DFUR 1200 mg/m^2 orally, day 4–7, 11–14, 18–21 and 25–28. Cycles were repeated as long as possible	*CF'*: Cisplatin 70 mg/m^2 i.v., on day 1; and 5'-DFUR 1200 mg/m^2 orally, days 4–7, 11–14, 18–21 and 25–28. Cycles were repeated as long as possible	33	29	1991–1996	Locally adv: 21.0% Metastatic: 79.0%	190 (16–1848)
Bouche (2004)[30]	*FLC*: Leucovorin 200 mg/m^2 i.v.; and bolus 5-FU 400 mg/m^2 i.v.; 5-FU 600 mg/m^2 i.v.; cisplatin 50 mg/m^2 i.v., on days 1 and 2. Cycles (15 days) were repeated every 14 days IFL: Irinotecan 180 mg/m^2 i.v.; 200 mg/m^2 i.v.; and bolus 5-FU 400 mg/m^2 i.v.; and 5-FU 600 mg/m^2 i.v. on days 1 and 2. Cycles (15 days) were repeated every 14 days	*FL*: Leucovorin 200 mg/m^2 i.v.; and bolus 5-FU 400 mg/m^2 i.v.; and 5-FU 600 mg/m^2 i.v. on days 1 and 2. Cycles (15 days) were repeated every 14 days	91	45	1999–2001	Metastatic: 98.5%	291 (17–1023)

Hawkins (2005)[31]	*DI*: Docetaxel 60 mg/m^2 i.v.; and irinotecan 250 mg/m^2 day 1. Cycles were repeated every 3 weeks	*DF*: Docetaxel 85 mg/m^2 i.v., day 1; and 5-FU 750 mg/m^2 i.v., day 1 through 5. Cycles were repeated every 3 weeks	43	43	1999–2000	Locally adv: 5.8% Metastatic: 94.2%	277.5 (7–931)
Moehler (2005)[12]	*IFL*: Irinotecan 80 mg/m^2 i.v.; leucovorin 500 mg/m^2 i.v.; and 5-FU 2000 mg/m^2 i.v., on days 1, 8, 15, 22, 29 and 36. Cycles were repeated every 7 weeks	*ELF*: folinic acid (leucovorin) 300 mg/m^2 i.v.; etoposide 120 mg/m^2; and bolus 5-FU 500 mg/m^2 i.v., for 3 consecutive days. The cycles were repeated every 22 days	58	62	2000–2003	Not supplied	271.5 (12–986)
Thuss-Patience (2005)[32]	*EpiCF*: Epirubicin 50 mg/m^2 i.v. day 1; cisplatin 60 mg/m^2 i.v. day 1; and 5-FU 200 mg/m^2 i.v., days 1 through 21. The cycles were repeated every 3 weeks	*DF*: Docetaxel 75 mg/m^2 i.v., day 1; and 5-FU 200 mg/m^2 i.v., days 1 through 21. Cycles were repeated every 3 weeks	45	47	1999–2002	Locally adv: 1.1% Metastatic: 93.6% Locally rec: 1.1%	286 (19–1138)
Ajani (2005)[33]	*DCF*: Docetaxel 60 mg/m^2 i.v. day 1; cisplatin 75 mg/m^2 i.v. day 1; and 5-FU 750 mg/m^2 i.v., days 1–5. The cycles were repeated every 3 weeks	*DC*: Docetaxel 85 mg/m^2 i.v. day 1; and cisplatin 75 mg/m^2 i.v. day 1. The cycles were repeated every 3 weeks	79	79	1998–1999	Locally adv: 3.2% Metastatic: 94.9% Locally rec: 1.9%	162 (6–690)
Van Cutsem (2006)[11]	*DCF*: Docetaxel 60 mg/m^2 i.v. day 1; cisplatin 75 mg/m^2 i.v. day 1; and 5-FU 750 mg/m^2 i.v., days 1 through 5. The cycles were repeated every 3 weeks	*CF*: Cisplatin 100 mg/m^2 i.v. day 1; and 5-FU 1000 mg/m^2 i.v., days 1 through 5. The cycles were repeated every 4 weeks	227	230	1999–2003	Locally adv: 2.2% Metastatic: 96.3% Locally rec: 0.4%	231 (1–1202)
Roth (2007)[34]	*EpiCF*: Epirubicin 50 mg/m^2 i.v. day 1; cisplatin 60 mg/m^2 i.v. day 1; and 5-FU 200 mg/m^2 i.v., days 1 through 21 *DCF*: Docetaxel 85 mg/m^2 i.v. day 1; cisplatin 75 mg/m^2 i.v. day 1; and 5-FU 300 mg/m^2 i.v., days 1–14	*DC*: Docetaxel 85 mg/m^2 i.v. day 1; and cisplatin 75 mg/m^2 i.v. day 1	82	39	1999–2003	Loco-regional: 33.6% Metastatic: 66.4%	279.5 (7–2001)
Dank (2008)[35]	*IFL*: Irinotecan 80 mg/m^2 i.v.; and leucovorin 500 mg/m^2 i.v. and 5-FU 2000 mg/m^2 i.v., on days 1, 8, 15, 22, 29 and 36. Cycles were repeated every 7 weeks	*CF*: Cisplatin 100 mg/m^2 i.v. day 1; and 5-FU 1000 mg/m^2 i.v., days 1 through 5. The cycles were repeated every 4 weeks	172	165	2000–2002	Locally adv: 1.8% Metastatic: 94.7% Locally rec: 0.6%	266 (9–1093)
Boku (2009)[36]	*IC*: Irinotecan 70 mg/m^2 i.v., on days 1 and 15; and cisplatin 80 mg/m^2 i.v., day 1. Cycles were repeated every 4 weeks After six cycles, the same dose of irinotecan alone was continued every 2 weeks *S*: S-1 40 mg/m^2 orally, twice a day for 4 weeks, followed by a 2-week rest	*F*: 5-FU 800 mg/m^2 i.v., daily for 5 days. Cycles were repeated every 4 weeks	470	234	2000–2006	Locally adv: 16.3% Metastatic: 64.2% Locally rec: 19.5%	354.5 (11–2621)
Total			2494 4245	1748			

Three of the patients were missing data for the allocated arm.

(HR = 0.97; 95%CI 0.87–1.09, 1461 patients from 10 trials[5,21–24,26,27,32,34]; 52% of 2561 targeted patients). No statistically significant heterogeneity was detected.

For platinum agents, analysis of 2337 patients from eight trials[8,24,26,28,30,32,35,36] (53% of 4369 targeted patients) showed a statistically significant difference in favour of the platinum-based regimen with regard to PFS (HR = 0.88; 95%CI 0.81–0.96) but not OS (HR = 0.96; 95%CI 0.88–1.05). There was, however, substantial heterogeneity between trials in terms of both PFS ($P < 0.0001$) and OS ($P = 0.021$). As a sensitivity analysis, we recomputed statistics without one study which had extreme results,[28] which showed a borderline benefit on OS (HR = 0.92, $P = 0.08$) while across-trial heterogeneity remained statistically significant for PFS ($P = 0.01$).

Analysis of taxanes from three trials[32–34] ($n = 667$, 69% of 971 targeted patients) showed no statistically significant difference with regard to either PFS (HR = 0.88; 95%CI 0.75–1.04) or OS (HR = 0.90; 95%CI 0.76–1.07). Some indication of heterogeneity was seen for PFS ($P = 0.05$) but not for OS ($P = 0.25$).

Finally, analysis of 1380 patients (5 trials;[12,30,31,35,36] 81% of 1698 targeted patients) showed a statistically significant benefit of irinotecan-based regimes over their comparator in terms of PFS (HR = 0.81; 95%CI 0.72–0.90) and a marginally non-significant benefit in terms of OS (HR = 0.90; 95%CI 0.80–1.01). No statistically significant heterogeneity was detected.

4. Discussion

The results of this IPD meta-analysis show that OS and PFS have been improved to a certain extent by the addition of experimental chemotherapeutic agents to pre-existing control or standard regimens, or by the introduction of more active agents such as platinum, taxanes or irinotecan. The benefits of the experimental treatments over their corresponding controls are hazard reductions of 13% for OS (HR = 0.87, $P < 0.0001$, Fig. 2) and 21% for PFS (HR = 0.79, $P < 0.0001$, eFig. 1). Although these overall relative risk reductions translate into only modest absolute improvements in median OS and PFS, they nevertheless confirm the benefit of chemotherapy for AGC, and justify further efforts at improving current regimens.

This overall analysis used all data collected, and is accordingly the most reliable from a statistical point of view. As it combines different comparisons, however, it lacks the specificity to reveal the benefits of individual agents. The results of the sub-analysis of adding a given chemotherapy to any chemotherapy confirm the results of the overall analysis, with a hazard reduction of 11% for OS ($P < 0.01$) and 26% for PFS ($P < 0.0001$). Although this analysis isolates the contribution of an additional agent, it does not address the issue of which agent is the most effective. Looking at individual agents suggests potential benefits of the most recent generations, namely cisplatin and irinotecan, but not of MMC or docetaxel. Results on the addition of anthracyclines deserve comment as they are inconsistent with the literature-based meta-analysis of Wagner, who found an OS benefit compared to a 5-FU–cisplatin association, based on three studies.[17] Our results were not restricted to a 5-FU + cisplatin comparator but also included two American trials using 5-FU + MeCCNU[5] and 5-FU[21] as controls. Further, our meta-analysis did not include one trial[46] comparing ECF to MCF ($n = 334$) with positive results of borderline significance. However, pooling the summary statistics of this latter trial with the collected IPD would not have modified the overall conclusion regarding the benefit of anthracyclines on OS.

Several limitations of this meta-analysis warrant mention. First, gastric cancers are heterogeneous, and it was therefore impossible to analyse the data according to important known prognostic factors, such as performance status and tumour type. Although a recent study suggested the importance of HER2 as the first biomarker for AGC,[66] a more useful classification for gastric cancer in terms of prognosis and predictive ability might be important. Similarly, our meta-analysis consists of a mixture of patients with proximal and distal cancer, and of different types of extension from local but unresectable tumours to visceral metastases involving liver, peritoneum, distant lymph nodes and bones.[67] This does not invalidate the value of this analysis but does underline the importance of more precise analyses of all subcategories of gastric tumours, which may have different natural histories and responses to treatment. Second, as far as PFS is concerned, some studies (mainly commercially-sponsored) performed CT scans at regular intervals until disease progression, whereas in other studies imaging was performed at the time of symptomatic progression rather than at pre-determined time-points.

Finally, we were only able to include data for 47% of the total number of patients from eligible randomised trials of AGC to date. This remains sub-optimal, given that IPD meta-analyses should be comprehensive and include all the trials ever conducted, whether positive or negative, or published or unpublished. While at present access to individual patient data is still very difficult, a consensus is emerging that such data should be made available to address subsequent research questions. In the United States, the National Institutes of Health Data Sharing Policy states that clinical trial 'data should be made as widely and freely available as possible while safeguarding the privacy of participants, and protecting confidential and proprietary data'.[68] Some journals have adopted a policy that trials of drugs and medical devices be considered for publication only if the authors commit to making the relevant anonymised patient level data available.[69] The pharmaceutical industry is also taking

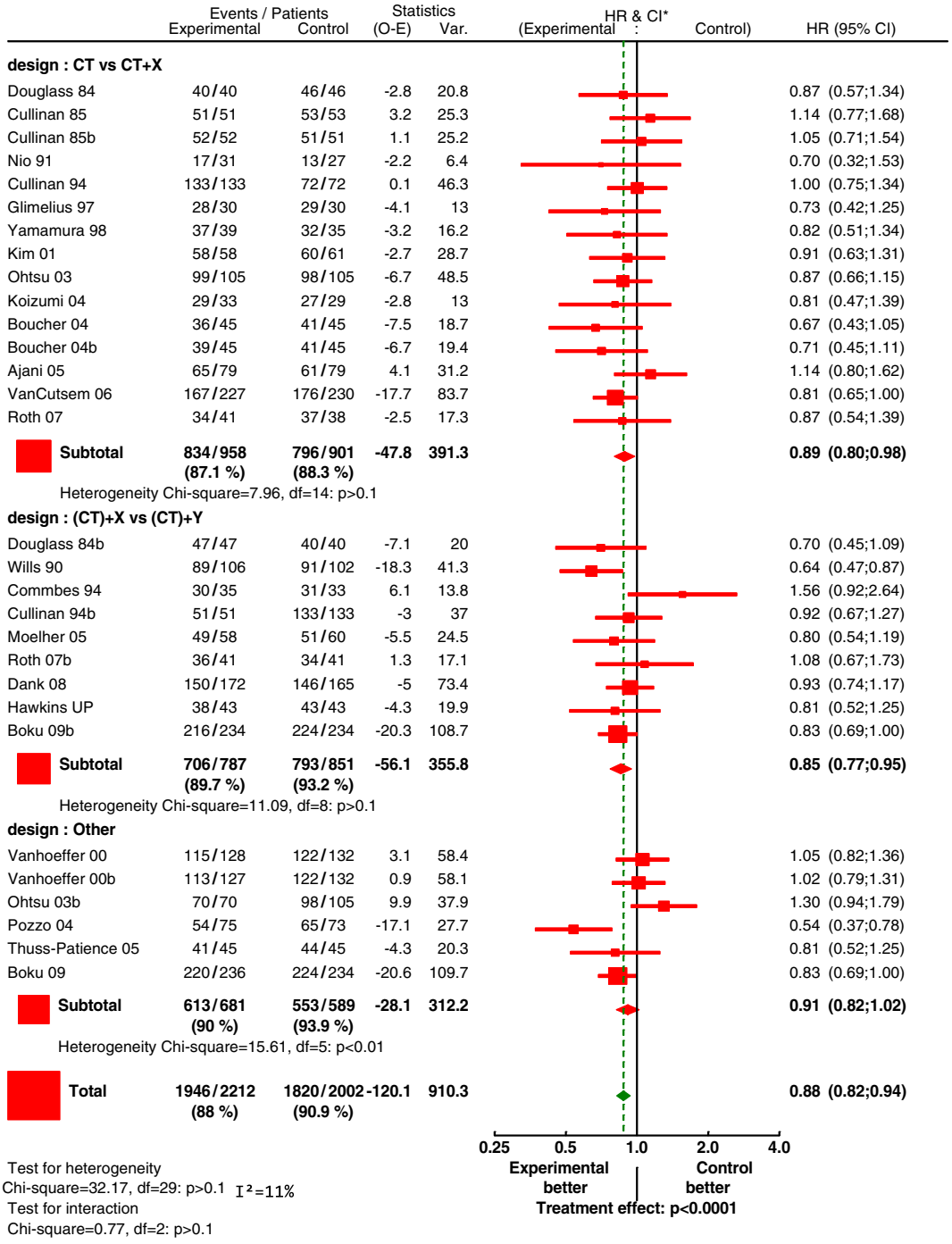

Fig. 2. Individual trial and overall hazard ratio for overall survival (OS) when comparing experimental arms versus control arms. $I^2 = 11\%$. The inverse of observed minus expected events measures the weight of each trial in the analysis. *P* values are from *P*-for-effect modification testing for heterogeneity within or across the groups of regimens. The sizes of data markers are proportional to the number of deaths in the trials. CI, confidence interval; HR, hazard ratio.

steps to making data from the trials they sponsor available for reasonable requests.[70] The GASTRIC collaboration favours any initiative to pool IPD since this provides the only reliable means to characterising the role of treatment specific regimens. Finally, as far as PFS is concerned, some studies (mainly commercially-sponsored) performed CT scans at regular intervals until disease progression, whereas in other studies imaging was performed at the time of symptomatic progression rather than at pre-determined time-points.

In conclusion, our IPD meta-analysis shows that OS and PFS have been modestly improved by the addition of experimental chemotherapeutic agents to pre-existing control or standard regimens. Nevertheless, median

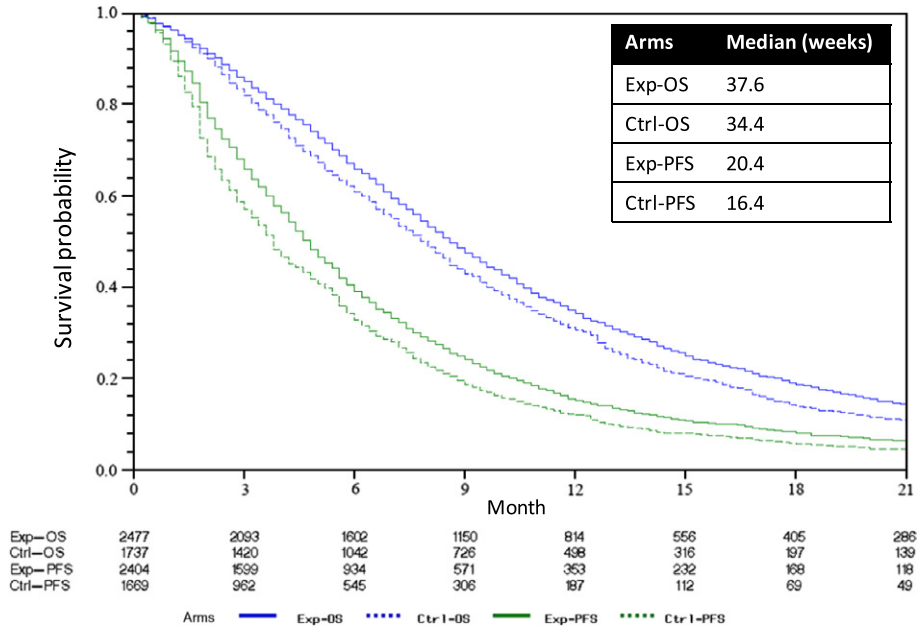

Fig. 3. Overall survival (OS) and progression-free survival (PFS) curves of investigational and control arms. Exp-OS, Experimental arm for OS; Ctrl-OS, Control arm for OS; Exp-PFS, Experimental arm for PFS; Ctrl-PFS, Control arm for PFS.

survival remains at less than 1 year for all investigated cytotoxic associations of chemotherapy, and none has emerged as a clear standard. We hope that molecularly targeted agents administered to subgroups of patients selected on the basis of biological characteristics may modify this disappointing situation.

Conflict of interest statement

This project was initiated under the auspices of the INCa, which served as a sponsor. The INCa did not participate in the design of the study. It participated in the conduct of the study at an earlier stage by centralising all the databases and by providing administrative and data management support. The sponsor had no role in the preparation, review or approval of the manuscript.

All members of the writing committee declare they have no conflict of interest with regard to this meta-analysis.

The corresponding author (Koji Oba) had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Oba and Paoletti contributed equally to this work.

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The GASTRIC Investigators:

Secretariat: Marc Buyse, Stefan Michiels, Koji Oba, Xavier Paoletti, Philippe Rougier, Seiichiro Yamamoto, Kenichi Nakamura.

Steering Committee: Yung-Jue Bang (Seoul National University College of Medicine, Seoul, Korea); Harry Bleiberg (Brussels, Belgium); Tomasz Burzykowski (Hasselt University, Diepenbeek, Belgium); Marc Buyse (International Drug Development Institute, Louvain-la-Neuve, Belgium); Catherine Delbaldo (Hôpital Louis Mourier, Colombes, France); Stefan Michiels (Jules Bordet institute, Brussels, Belgium); Satoshi Morita (Yokohama City University, Kanagawa, Japan); Koji Oba (Hokkaido University, Hokkaido, Japan); Yasuo Ohashi (University of Tokyo, Tokyo, Japan); Xavier Paoletti (Institut Curie, Paris, France); Jean-Pierre Pignon (Institut Gustave-Roussy, Villejuif, France); Philippe Rougier (University Hospital Europeen Georges Pompidou [AP-HP], Boulogne, France); Junichi Sakamoto (Nagoya University, Aichi, Japan); Daniel Sargent (Mayo Clinic, Rochester, Minnesota, USA); Mitsuru Sasako (Hyogo College of Medicine, Hyogo, Japan); Eric Van Cutsem (Digestive Oncology Unit, University Hospital Gasthuisberf, Leuven, Belgium).

Collaborators: J Ajani, N Boku, C Barone, M Borner, O Bouche, R Bugat, C Coombes, S Cullinan, M Dank, H Douglass, N Fuse, B Glimelius, R Hawkins, S Kanzler, W Koizumi, TW Kim, F Lordick, M Moehler, Y Nio, A Ohtsu, C Pozzo, P Reichardt, A Roth, C Schumacher,

K Shitara, P Thuss-Patience, A Tsuburaya, E Van Cutsem, U Vanhoefer, J Wils, Y Yamamura.

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Appendix A. Writing committee

Koji Oba PhD (Translational Research and Clinical Trial Center, Hokkaido University Hospital, Hokkaido, Japan), Xavier Paoletti PhD (Institut Curie/ Inserm U900, Paris, France), Yung-Jue Bang MD PhD (Seoul National University College of Medicine, Seoul, Korea), Harry Bleiberg MD PhD (Jules Bordet, Brussels, Belgium), Tomasz Burzykowski PhD (Hasselt University, Diepenbeek, Belgium), Nozomu Fuse MD PhD (National Cancer Center Hospital East, Chiba, Japan), Stefan Michiels PhD (Jules Bordet institute, Brussels, Belgium), Satoshi Morita PhD (Yokohama City University, Kanagawa, Japan), Yasuo Ohashi PhD (University of Tokyo, Tokyo, Japan), Jean-Pierre Pignon MD, PhD (Institut Gustave-Roussy, Villejuif, France), Philippe Rougier MD, PhD (University Hospital Europeen Georges Pompidou (AP-HP), Paris, France), Junichi Sakamoto MD, PhD (Nagoya University, Aichi, Japan), Daniel Sargent PhD (Mayo Clinic, Minnesota, USA), Mitsuru Sasako MD, PhD (Hyogo College of Medicine, Hyogo, Japan), Kohei Shitara MD PhD (Aichi Cancer Center Hospital, Aichi, Japan), Akira Tsuburaya MD PhD (Kanagawa Cancer Center Hospital, Kanagawa, Japan), Eric Van Cutsem MD, PhD (Digestive Oncology Unit, University Hospital Gasthuisberf, Leuven, Belgium), Marc Buyse PhD (International Drug Development Institute, Louvain-la-Neuve, Belgium).

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2012.12.016.

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