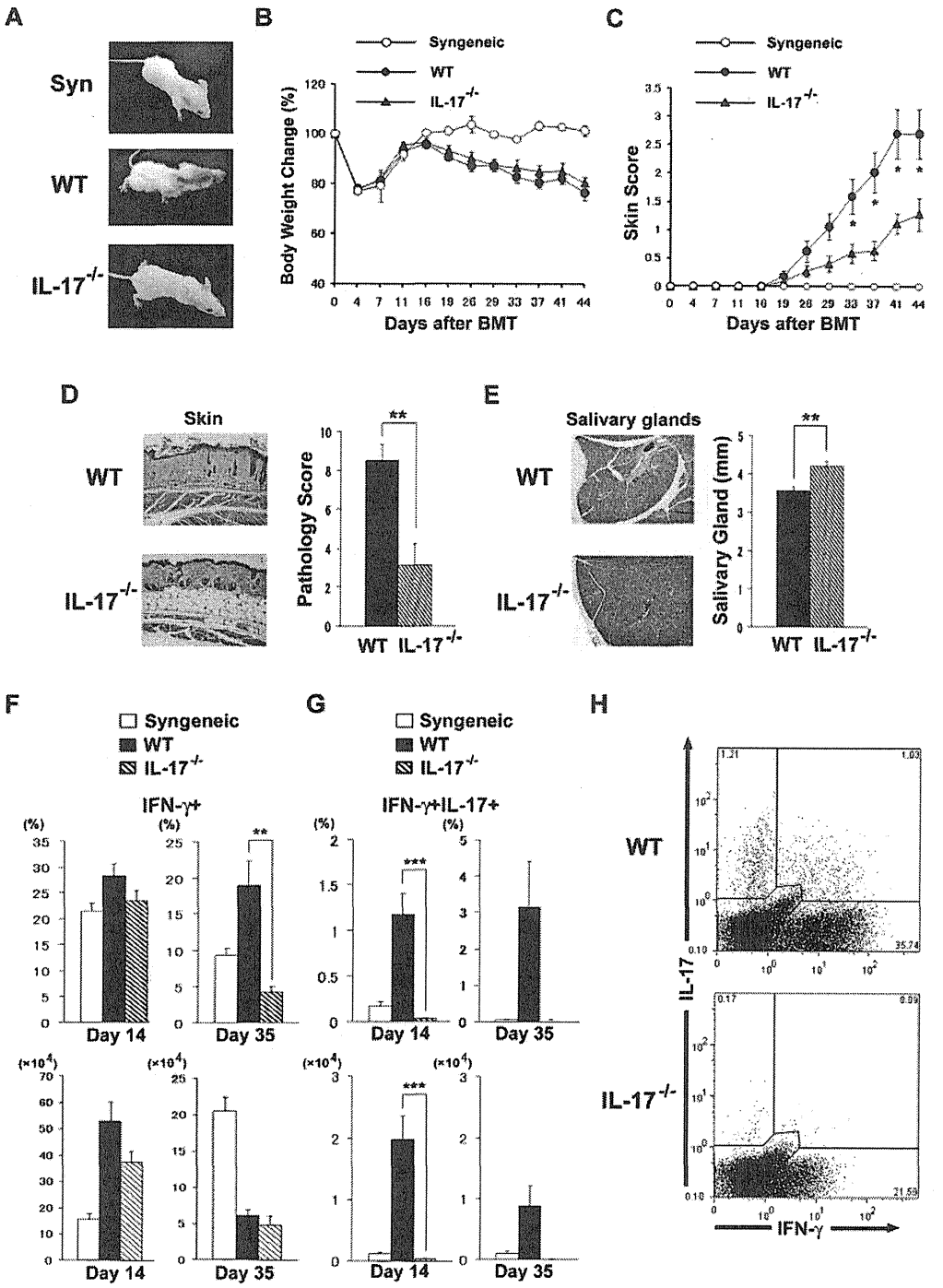

Figure 2. IL-17$^{-/-}$ donor T cells ameliorate cGVHD. Sublethally irradiated BALB/c recipients were transplanted from WT, IL-17$^{-/-}$ B10.D2, or syngeneic BALB/c donors. (A) Gross observation of the skin lesions from recipients of syngeneic, WT, and IL-17$^{-/-}$ donors 28 days after BMT. The recipients were analyzed for body weight (B) and cGVHD skin scores (C); data from 2 independent experiments were combined (n = 14 per group). Pathology score of skin (D) and the longest diameter of the salivary gland (E) on day 35 of BMT are shown. Four to 6 recipients were examined in each group. (F-G) PLN cells of the recipients of syngeneic (white bar), WT (black bar), or IL-17$^{-/-}$ (striped bar) donors were stained for intracellular IFN-γ and IL-17 on days 14 and 35 after BMT. The percentages and absolute numbers of IFN-γ$^+$ cells (F) and IFN-γ$^+$/IL-17$^+$ cells (G) are shown. Data from 2 replicated experiments were combined (n = 6-11 per group). (H) Representative staining for intracellular IFN-γ and IL-17 on CD4$^+$ T cells of WT or IL-17$^{-/-}$ mice on day 35 is shown. Data represent the means ± SEs. *$P \leq .05$, **$P \leq .01$, and ***$P \leq .001$.

Administration of Am80 ameliorates cGVHD

Next, we examined whether ATRA or Am80 can down-regulate cGVHD. BALB/c recipients were orally administered ATRA (200 μg/mouse) or Am80 from day 0 of BMT. We found that ATRA tended to decrease the clinical cGVHD score (Figure 5A), whereas Am80 significantly ameliorated the clinical score compared with controls ($P = .01$; Figure 5B). Histopathologic examination of the skin on day 16 showed significantly reduced cGVHD damage in Am80-treated animals (day 16, 4.8 ± 0.4 vs 7.4 ± 0.4; $P < .01$; Figure 5C), No differences were observed in pathology scores of the lung, liver, or colon between the 2 groups (Figure 5C). Because it has been reported that Am80 can induce Treg cells,[29] we

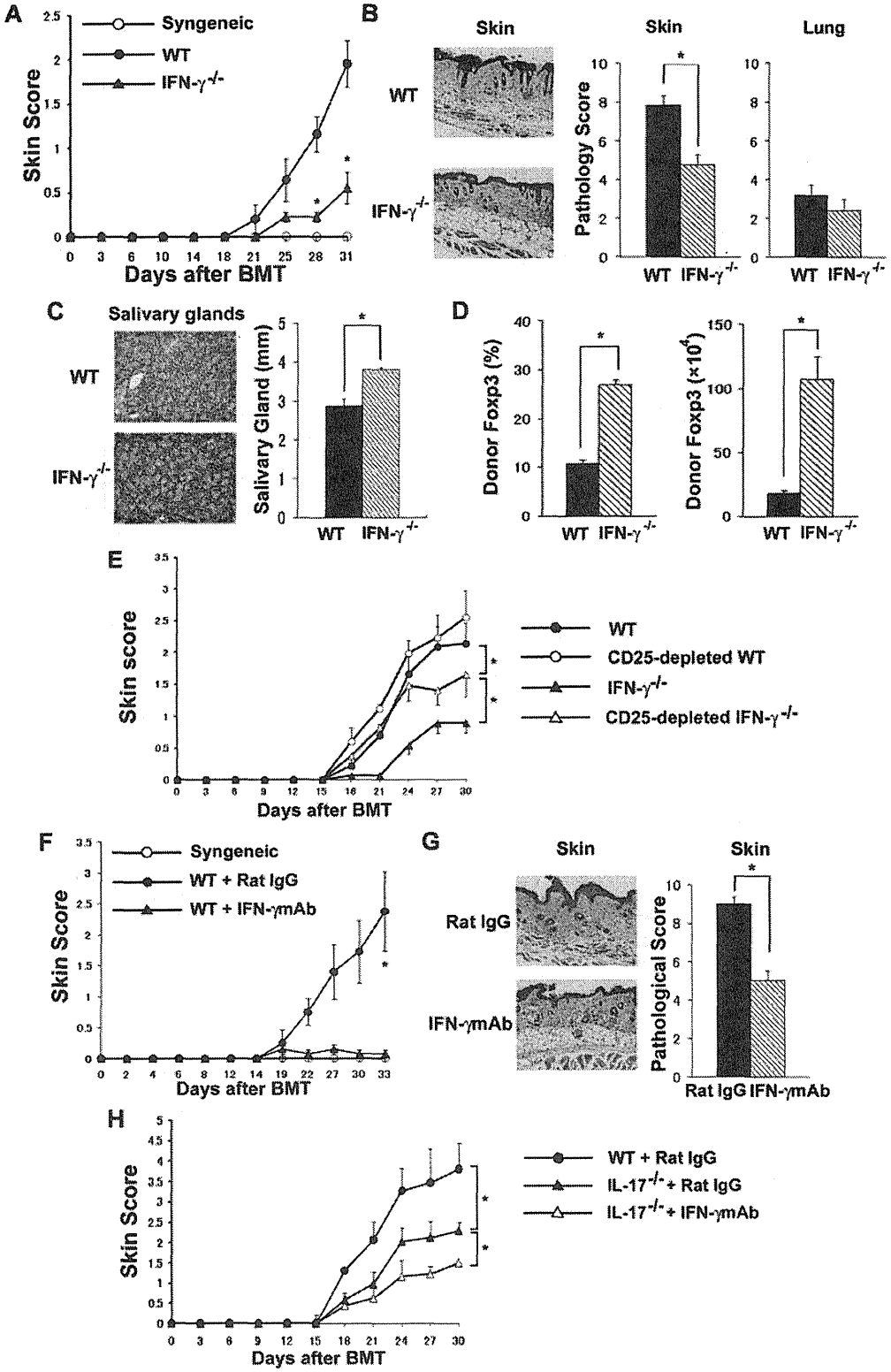

Figure 3. Donor Th1 differentiation and IFN-γ production are responsible for exacerbated cGVHD. (A-D) Sublethally irradiated BALB/c recipients were transplanted from WT or IFN-$\gamma^{-/-}$ B10.D2 donors. Clinical skin cGVHD scores (A), pathology score of skin and lung (B), and the longest diameter of the salivary gland (C) on day 35 after BMT are shown. Four to 6 recipients were examined in each group. Data are from 1 representative of 3 independent experiments. (D) PLN cells of the recipients on day 35 were stained for intracellular Foxp3. The percentages and the absolute number of $CD4^+Foxp3^+$ Treg cells are shown. Four to 6 recipients were examined in each group. Data are from 1 representative of 2 independent experiments. (E) Sublethally irradiated BALB/c recipients were transplanted 8×10^6 TCD-BM cells plus 2×10^6 total spleen T cells or CD25-depleted T cells from WT or IFN-$\gamma^{-/-}$ B10.D2 donors. The skin cGVHD scores are shown ($n = 6$ per group). Data are from 1 representative of ≥ 2 independent experiments. (F-H) Sublethally irradiated BALB/c recipients were transplanted from WT or IL-$17^{-/-}$ B10.D2 donors. The recipients were injected with anti–IFN-γ mAbs or rat IgG (160 μg/mouse) on days 0, 5, 10, and 15 after BMT and were assessed for the clinical signs of cGVHD every 3 days. The clinical skin cGVHD scores (F), histopathology, and pathology score of the skin (G) on day 35 of BMT from WT donors. Four mice per group were used. Data are from 1 representative of ≥ 2 repeated experiments. (H) The clinical skin cGVHD scores after BMT from WT or IL-$17^{-/-}$ donors are shown. Six mice per group were used. Data are from 1 representative of 2 independent experiments. The means (± SEs) of each group are shown; *$P < .05$.

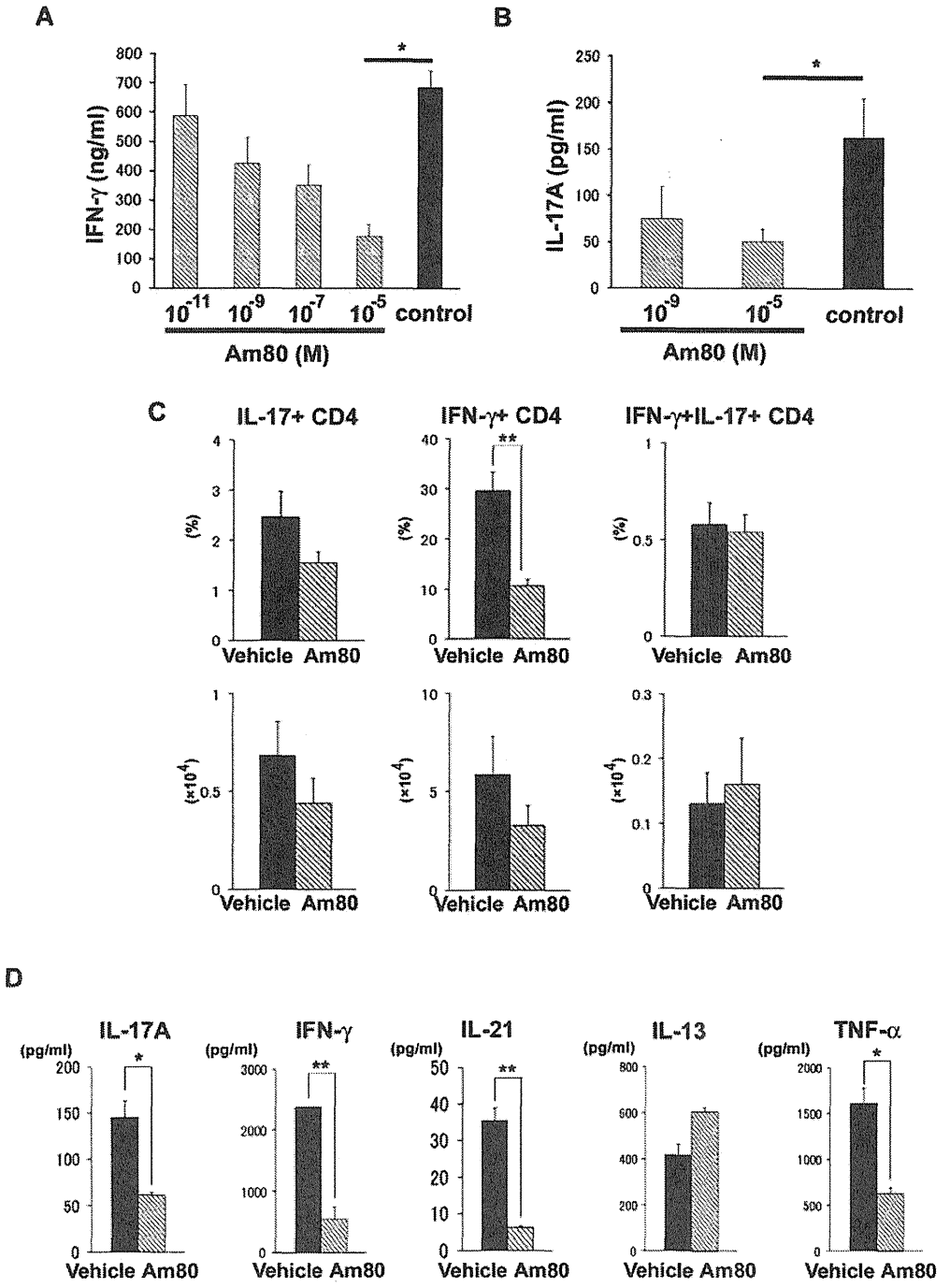

Figure 4. Am80 inhibits donor Th1 and Th17 cells in vitro and in vivo. Sublethally irradiated BALB/c recipients were transplanted from WT B10.D2 donors. (A-B) PLN cells from recipients (n = 3-6 per group) on day 14 were treated with Am80 or vehicle solution for 24 hours, the supernatants were collected, and ELISA was performed to determine the cytokine levels. Graphs represent the levels of cytokines secreted per 1×10^6 whole stimulated PLN cells. The data are from 1 representative of ≥ 3 independent experiments. (C-D) After BMT, recipients (n = 4-6 per group) were administered oral Am80 (1.0 mg/kg of body weight) or vehicle solution daily from day 0. PLNs of the recipients were stained for intracellular IFN-γ and IL-17. (C) The percentage and absolute number of IFN-γ$^+$ and IL-17$^+$–producing CD4$^+$ T cells. Data are from 1 representative of ≥ 2 repeated experiments. (D) PLN cells from recipients (n = 3-6 per group) treated with Am80 or vehicle on day 16 were stimulated with PMA and ionomycin. Five hours later, the supernatants were collected to determine cytokine levels by CBA. Graphs represent the levels of cytokines secreted per 1×10^6 whole stimulated PLN cells. The data are from 1 representative of ≥ 3 independent experiments. The means (± SEs) of each group are shown; *$P < .05$ and **$P < .01$.

quantified the frequency of Foxp3-expressing CD4$^+$ T cells in the PLNs after BMT. Recipients administered Am80 showed a decreased frequency of Foxp3$^+$ cells (day 17, 12.3% ± 2.5% vs 23.5% ± 2.6%; $P = .02$; Figure 5D). Foxp3 mRNA expression of the target organ (the ear) was also decreased in the Am80 recipients (data not shown). To confirm that the effects of Am80 are independent of Treg cells, mice were injected with whole T cells or CD25-depleted T cells from donors. As shown in Figure 5E, depletion of CD25$^+$ cells from the donor inoculum did not exacerbate skin cGVHD in Am80-treated mice, thus suggesting that the effects of Am80 treatment are not associated with Treg cells.

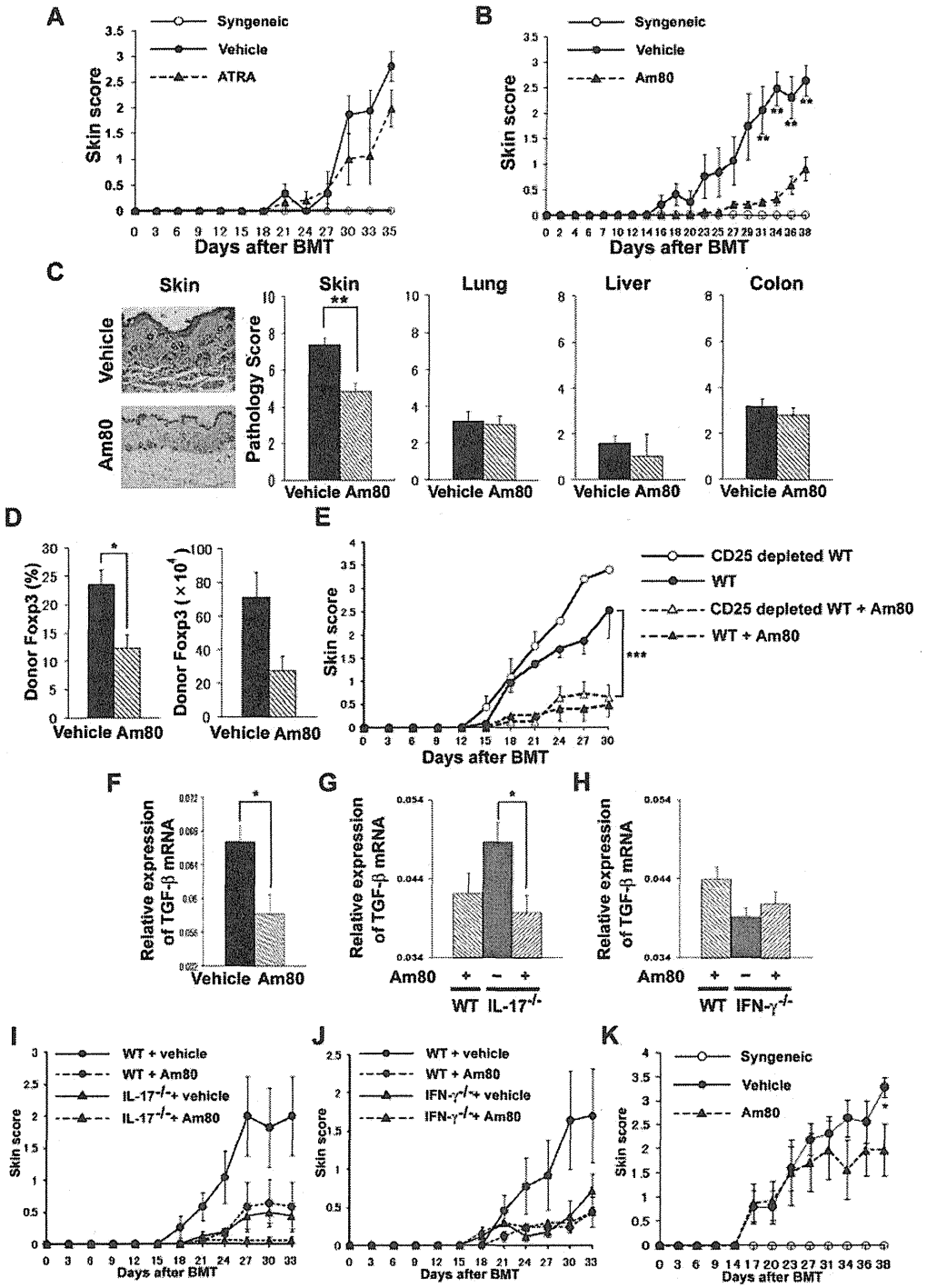

Figure 5. Administration of Am80 ameliorates cGVHD. (A-D) Sublethally irradiated BALB/c recipients were transplanted from WT B10.D2 donors. The recipients received daily administration of ATRA (200 μg/mouse; A), Am80 (1.0 mg/kg of body weight; B), or vehicle solution orally after BMT and were assessed for clinical signs of cGVHD every 3 days. The skin cGVHD scores are shown. (C) Representative histopathology of skin and pathology score of skin, lung, liver, and colon in each group (n = 5-6 per group) on day 16 after BMT are shown. (D) PLN cells of the recipients on day 16 were stained for intracellular Foxp3. The percentages and absolute numbers of $CD4^+Foxp3^+$ Treg cells are shown. Data are from 1 representative of ≥ 2 independent experiments. (E) Sublethally irradiated BALB/c recipients were transplanted with 8×10^6 TCD-BM cells plus 2×10^6 total spleen T cells or CD25-depleted T cells from WT or IFN-$\gamma^{-/-}$ B10.D2 donors. After BMT, recipients were given Am80 or vehicle solution. The skin cGVHD scores are shown. There were 6 recipients in each group; the data are from 1 representative of ≥ 2 independent experiments. (F-K) Sublethally irradiated BALB/c recipients were transplanted from WT (F), IL-$17^{-/-}$ (G), and IFN-$\gamma^{-/-}$ (H) donors. After BMT, recipients were given Am80 or vehicle solution. TGF-β mRNA expression in the ears on day 35 after BMT (F-H) and skin cGVHD scores (I-J) are shown. Data are from 1 representative of ≥ 2 independent experiments (n = 5 per group). (K) The skin cGVHD scores of BMT recipients treated with Am80 or vehicle solution orally daily after day 21 of BMT; data from 3 independent experiments were combined (n = 12-14 per group). $^*P < .05$, $^{**}P < .01$, and $^{***}P < .005$.

TGF-β is a critical mediator of fibrosis in cGVHD skin lesions.[30] TGF-β mRNA expression was decreased in the ear of the Am80 recipients (day 17, $P = .02$; Figure 5F). We then assessed TGF-β mRNA expression in recipients of IL-$17^{-/-}$ or IFN-$\gamma^{-/-}$

donors treated with Am80. Am80 further reduced skin scores and TGF-β expression in recipients of IL-17$^{-/-}$ donors (Figure 5G-I) but not in recipients of IFN-γ$^{-/-}$ donors (Figure 5H,J). These results suggest that the effects of Am80 are more dependent on IFN-γ than on IL-17.

Finally, we examined whether Am80 could be used for the treatment of cGVHD. Am80 was orally administered to mice from day 21 of BMT, when mice had developed clinical signs of cGVHD. Am80 significantly improved clinical scores ($P = .016$; Figure 5K).

Discussion

The results of the present study showed that Th1 and Th17 cells contribute to cGVHD with the use of a MHC-compatible, miHA-incompatible model of cGVHD. In addition, we demonstrated that Am80 down-regulates both Th1 and Th17 cells in vitro and in vivo, resulting in attenuation of cGVHD.

For many years, the best defined subsets of effector T cells of the CD4$^+$ Th lineage were the Th1 and Th2 cells. A third subset of CD4$^+$ effector cells was identified and named Th17 cells, because the signature cytokine that they produce is IL-17.[31] Although the role of Th17 in acute GVHD has been evaluated by several groups with inconsistent results,[32-35] few studies have addressed the role of Th17 in cGVHD. Initially, cGVHD was hypothesized to be a Th2-mediated disease on the basis of the results in a nonirradiated P→F1 model of cGVHD. cGVHD in this model is mediated by host B-cell autoantibody production stimulated by donor Th2 cells. Th1 polarization of donor T cells activates donor CD8$^+$ CTLs to kill host B cells, resulting in amelioration of cGVHD.[36] However, the relevance of this model is unclear in clinical BMT in which host B cells are eliminated by conditioning. Such different effector mechanisms between the models may be associated with distinct requirement of Th subsets for cGVHD between the studies. In the present study, we assessed the kinetics of Th1, Th2, and Th17 cells during the development of cGVHD in the B10.D2→BALB/c model. Th1 and Th2 responses were up-regulated early after BMT, followed by a subsequent up-regulation of Th17 cells. Significantly greater numbers of Th17 cells were detected in the lung and liver from allogeneic recipients than in those from syngeneic recipients. We then evaluated the role of Th17 in cGVHD with the use of IL-17$^{-/-}$ mice as several groups had used,[32-34,37,38] although interpretation of the results deserves caution because the Th17 lineage is uniquely regulated by RORγt,[13,14] and other cytokines such as IL-21 and IL-22 produced by Th17 cells may also contribute to Th17-mediated GVHD. On transfer of IL-17$^{-/-}$ B10.D2 donor T cells, cGVHD was significantly ameliorated compared with that in recipients of WT T cells, suggesting that Th17 contributes to cGVHD in this model. In particular, Th17 plays a significant role in skin cGVHD. This agrees with the recent observation by Hill et al[37] that donor pretreatment with G-CSF induces Th17 differentiation of donor T cells and induces skin GVHD after peripheral blood stem cell transplantation. In an adoptive transfer model of autoimmune cGVHD, Th17 cells infiltrated target tissues.[39] However, a subsequent study showed the absence of donor Th17 cells did not abrogate GVHD pathology,[38] in contrast to our results. In the absence of donor IL-17, Th1 responses were preserved in that study but were reduced in our study. Such difference in Th1 responses may produce different outcomes between the studies. In mouse models of acute GVHD, Yi et al showed enhanced Th1 differentiation of donor T cells by increased production of IL-12 from dendritic cells in the absence of IL-17.[33] By contrast, Kappel et al showed reduced numbers of IFN-γ–positive CD4$^+$ T cells and IFN-γ secretion in culture in the absence of IL-17.[34] These results together with our results suggest that IL-17 may induce IFN-γ, although such a hierarchy of Th1/Th17 pathways may be context or model dependent or both and will need to be studied in the future. Nonetheless, it should be noted that cGVHD still developed in the absence of donor IL-17 cells in our study. Taken together, it is probable that Th17 is not an absolute requirement for cGVHD, and either Th1 or Th17 is sufficient to cause cGVHD.

We demonstrated that IFN-γ$^{-/-}$ donor mice and injecting anti–IFN-γ mAb ameliorated cGVHD. Thus, Th1 and Th17 responses play a pathogenic role in cGVHD in this model. These results were consistent with a recent study reporting that cGVHD is mediated by Th1 and Th17 responses because of the progressive loss of CD4$^+$CD25$^+$Foxp3$^+$ T cells during acute GVHD in mice.[39] These results were also consistent with clinical studies showing that Th1 cells and Th17 cells increased in patients with active cGVHD.[40-43] Increased transcription of IFN-γ has also been detected in the affected skin and oral mucosa of patients with cGVHD.[41,44] In this study, we found no differences in Th17 cells between IFN-γ$^{-/-}$ and WT recipients, although significantly greater numbers of Treg cells were detected in IFN-γ$^{-/-}$ recipients. CD25-depleted T cells from IFN-γ$^{-/-}$ mice induced more severe skin cGVHD compared with CD25-replete IFN-γ$^{-/-}$ T cells, but still less severe cGVHD compared with CD25-depleted T cells from WT mice (Figure 3E), suggesting that IFN-γ contributes to the pathogenesis of cGVHD by both Treg-independent and -dependent pathways. Neutralization of IFN-γ ameliorated cGVHD in the absence of donor IL-17 (Figure 3H), suggesting again that both Th1 and Th17 responses contribute to the pathogenesis of cGVHD.

We found that donor-derived Th17 cells were generated in recipients of syngeneic transplantation in addition to allogeneic transplantation. However, the kinetics of Th17 development differed between the syngeneic and allogeneic settings; Th17 cells developed in the early phase after syngeneic transplantation. Kappel et al speculated that Th17 development may be the result of increased immune reconstitution of syngeneic hosts compared with allogeneic hosts with GVHD.[34] We additionally identified a population of donor-derived IFN-γ$^+$IL-17$^+$ cells after allogeneic BMT. It has been shown that a subset of IL-17–producing cells can also produce IFN-γ in vivo.[34,45] Such CD4$^+$IFN-γ$^+$IL-17$^+$ T cells have been postulated to play a causative role in the pathogenesis of experimental autoimmune encephalomyelitis (EAE).[46] IFN-γ$^+$IL-17$^+$ cells were only detected after allogeneic BMT, but not after syngeneic BMT, suggesting that this population is generated by allogeneic stimulation, but not because of lymphopenia-induced proliferation. Further investigations are required to clarify the difference in function between IL-17 single-positive and IFN-γ/IL-17 double-positive cells.

ATRA suppresses Th17 differentiation and effector function by RARα signaling,[18] but ATRA can also bind to RARβ and RARγ, which can form a variety of homodimers and heterodimers with 3 retinoid X receptors.[15] Nonselective receptor binding is thought to be a main cause of the side effects associated with the administration of ATRA and other pan-RAR agonists. Am80 is a synthetic RAR agonist that shows high affinity to RARα/β. In addition to a greater specificity for RARα, Am80 offers several other advantages over ATRA as a therapeutic agent, including less toxicity, greater stability, fewer potential side effects, and superior bioavailability. Am80 is effective in autoimmune disease models of collagen-induced arthritis,[20,47] EAE,[21,29] 2,4-dinitrofluorobenzene–

induced contact dermatitis,[22] and atherosclerosis.[23] Because retinoids can down-regulate Th1 and Th17 cells and can ameliorate autoimmune diseases, we hypothesized that these retinoids would attenuate cGVHD. We demonstrated that Am80 down-regulated Th1 and Th17 differentiation of donor T cells in BALB/c recipients of B10.D2 donors, resulting in reduced cGVHD. Our results suggest that combined blockade of Th1 and Th17 responses may represent a promising strategy to prevent or treat cGVHD, as has been suggested for acute and chronic GVHD.[32,39,48] Most recently, Yu et al used mice deficient for both T-bet and RORγt as T-cell donors and clearly showed that blockade of both Th1 and Th17 differentiation is required to prevent acute GVHD.[14] In addition, TGF-β mRNA expression in the skin decreased in the Am80 recipients of WT and IL-$17^{-/-}$ but not IFN-$\gamma^{-/-}$ donors. These results suggest that Am80 down-regulates TGF-β and that this effect is more dependent on IFN-γ than on IL-17. Unexpectedly, those recipients administered Am80 had a significantly lower frequency of $Foxp3^+$ cells. These results differ from those of in vitro studies performed by Mucida et al,[28] in which retinoic acids were shown to be capable of inhibiting the IL-6–driven induction of Th17 cells and to promote Treg cell differentiation. Thus, retinoic acids enhance Treg differentiation and inhibit both Th17 and Th1 in vitro; however, the effects of retinoids may be more complex in vivo, because retinoids can affect not only T cells but also other immunoregulatory cells. For example, previous in vivo studies reported that Am80 suppressed Treg cells in experimental models of EAE[29] and collagen-induced arthritis,[47] similar to our study. In our study, Am80 suppressed TGF-β expression, a key cytokine in Treg development, which may have resulted in the suppression of Treg.

In conclusion, both Th1 and Th17 contribute to the development of cGVHD. Am80 down-regulates TGF-β and also regulates both Th1 and Th17 cells in vitro and in vivo, resulting in attenuation of cGVHD. Thus, administration of Am80, which is currently available as medication for acute promyelocytic leukemia in Japan,[49] may represent effective strategy for prevention and treatment of cGVHD.

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Authorship

Contribution: H.N. conducted the experiments, analyzed the data, and wrote the manuscript; Y.M. designed the experiments, supervised the research, and wrote the manuscript; H.S., K.K., Y.Y., S.K., and H.U. performed the research; K.T., T. Tanaka, and T.Y. performed histopathologic analyses of the organs; Y.I. provided vital new reagents for the study; and T. Teshima and M.T. supervised the research.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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ORIGINAL REPORT

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

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ABSTRACT

Purpose
This phase III study compared treatment with weekly paclitaxel and biweekly irinotecan in patients with advanced gastric cancer refractory to treatment with fluoropyrimidine plus platinum.

Patients and Methods
Patients were randomly assigned to receive either paclitaxel (80 mg/m^2 on days 1, 8, and 15, every 4 weeks) or irinotecan (150 mg/m^2 on days 1 and 15, every 4 weeks). Primary end point was overall survival (OS), and secondary end points were progression-free survival (PFS), response rate, adverse events, and proportion of patients who received third-line chemotherapy.

Results
Of 223 patients, 219 were eligible for analysis. Median OS was 9.5 months in 108 patients allocated to the paclitaxel group and 8.4 months in 111 patients allocated to the irinotecan group (hazard ratio [HR], 1.13; 95% CI, 0.86 to 1.49; P = .38). Median PFS was 3.6 months in the paclitaxel group and 2.3 months in the irinotecan group (HR, 1.14; 95% CI, 0.88 to 1.49; P = .33). Response rate was 20.9% in the paclitaxel group and 13.6% in the irinotecan group (P = .24). Common grade 3 to 4 adverse events were neutropenia (paclitaxel group, 28.7%; irinotecan group, 39.1%), anemia (21.3%; 30.0%), and anorexia (7.4%; 17.3%). Treatment-related deaths occurred in two patients (1.8%) in the irinotecan group. Third-line chemotherapy was administered in 97 patients (89.8%) after paclitaxel treatment and in 80 patients (72.1%) after irinotecan treatment (P = .001).

Conclusion
No statistically significant difference was observed between paclitaxel and irinotecan for OS. Both are reasonable second-line treatment options for advanced gastric cancer.

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INTRODUCTION

The outcomes in patients with unresectable gastric cancer are extremely poor; median survival times of 3 to 5 months have been reported with best supportive care (BSC) alone.[1-3] In randomized studies conducted in the 1990s, first-line chemotherapy for advanced gastric cancer provided survival benefit over BSC alone. After many clinical trials, at present, fluoropyrimidine plus platinum with or without epirubicin or docetaxel is regarded as standard first-line chemotherapy in the treatment of gastric cancer worldwide.[4-9]

Since S-1 was approved for treatment of advanced gastric cancer in Japan, several phase III studies have been conducted, such as the JCOG 9912 (Japan Clinical Oncology Group 9912; fluorouracil *v* S-1 *v* irinotecan plus cisplatin),[10] SPIRITS (S-1 Plus Cisplatin Versus S-1 in a Randomized Controlled Trial in the Treatment for Stomach Cancer; S-1 *v* S-1 plus cisplatin),[9] and GC0301/TOP-002 trials (Gastric Cancer 0301/Topotecin-002; S-1 *v* S-1 plus irinotecan).[11] On the basis of these study results, S-1 plus cisplatin is accepted as standard first-line chemotherapy for advanced gastric cancer

in Japan. Despite no robust evidence of survival benefit, > 70% of participants received second-line chemotherapy in these studies.[9-11]

Many phase II studies of second-line chemotherapy for advanced gastric cancer have been conducted.[12-20] In evaluations of taxanes, administration of both paclitaxel (210 mg/m^2) and docetaxel (60 mg/m^2) on a triweekly schedule resulted in high rates of grade 3 or 4 neutropenia (37% to 88%),[12-14] whereas lower rates of severe neutropenia (3% to 32%) were observed with weekly administration of paclitaxel (80 mg/m^2).[15-18] Regarding efficacy parameters, response rate (RR) and progression-free survival (PFS) were similar for patients on the triweekly and weekly schedules of paclitaxel. Two reports evaluated weekly paclitaxel as second-line chemotherapy, in which median overall survival (OS) was 5 and 6.9 months, respectively.[15,16] In other studies, combination chemotherapy including biweekly administration of irinotecan (150 mg/m^2) as second-line chemotherapy resulted in median OS of 8 to 10 months,[19,20] although toxicity seemed to be more severe than that seen with weekly paclitaxel. Thus, weekly paclitaxel has become the preferable second-line chemotherapy in Japan.

At present, taxanes and irinotecan are two main options for treatment of advanced gastric cancer refractory to fluoropyrimidine plus platinum. However, to our knowledge, no randomized study has directly compared the efficacy of these two treatments. The West Japan Oncology Group (WJOG) conducted a phase III trial (WJOG 4007) comparing paclitaxel with irinotecan in patients with advanced gastric cancer.

PATIENTS AND METHODS

Patients

Eligible patients were age 20 to 75 years with histologically confirmed metastatic or recurrent gastric adenocarcinoma. Other inclusion criteria were Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2; disease progression confirmed by computed tomography (CT), endoscopy, or other imaging technique during or within 1 month after last dose of first-line chemotherapy with fluoropyrimidine plus platinum; no prior chemotherapy with taxanes or irinotecan; and no severe peritoneal metastasis. Severe peritoneal metastasis was defined as ileus or subileus suggested on barium enema examination and moderate to severe ascites exceeding the pelvic cavity on spine CT scan caused by peritoneal metastasis. In case of treatment with adjuvant or neoadjuvant chemotherapy consisting of fluoropyrimidine plus platinum, patients with disease progression during treatment or within 6 months after treatment completion were eligible. Adequate bone marrow, hepatic, and renal functions were also required.

Study Design

WJOG 4007 was a prospective, multicenter, randomized, open-label, parallel-group phase III clinical trial conducted at 37 centers in Japan. The protocol was approved by the independent ethics committee or institutional review board of each participating institution. This trial was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before study entry. The trial was registered with the University Hospital Medical Information Network.

After checking eligibility, patients were randomly assigned at a 1:1 ratio to receive either paclitaxel or irinotecan. Random assignment was carried out centrally at the data center using minimization method with the following adjustment factors: institution, ECOG PS (0 to 1 *v* 2), and measurable lesions (presence *v* absence). Neither investigators nor patients were blinded to the allocated treatment.

Treatment

Paclitaxel (80 mg/m^2) was administered intravenously on days 1, 8, and 15, every 4 weeks. Patients were premedicated with histamine receptor-1 and -2 blockers and dexamethasone for prophylaxis of allergic reactions 30 minutes before paclitaxel administration. Irinotecan (150 mg/m^2) was administered intravenously on days 1 and 15, every 4 weeks. Dose reduction and/or cycle delays were permitted according to predefined toxicity criteria. Treatment continued until disease progression, occurrence of unacceptable serious toxicity, or patient refusal of further treatment. Subsequent chemotherapy was not specified.

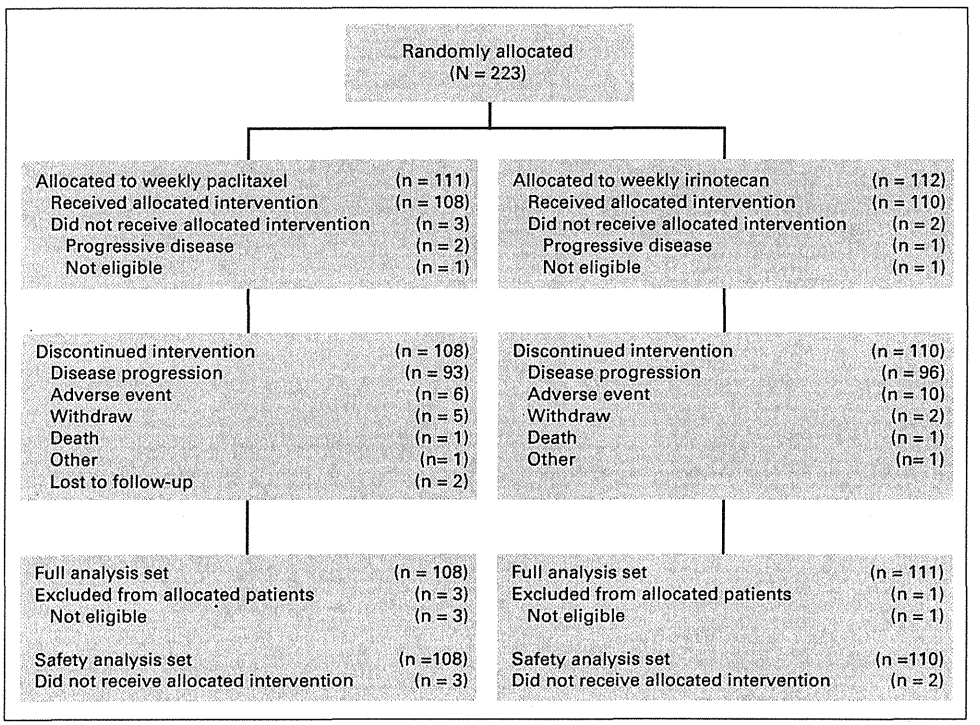

Fig 1. CONSORT diagram.

Assessments

Vital signs, ECOG PS, and laboratory tests were assessed within 7 days before study entry. Physical examinations and hematology and biochemistry tests were conducted during drug administration throughout the treatment course. Tumor assessments using CT scans of the chest, abdomen, and pelvis were performed within 28 days before study entry and repeated every 2 months after random assignment until discontinuation of protocol treatment. RECIST (version 1.0) was used to evaluate treatment responses.[21] Safety assessments were repeated every 2 weeks until initiation of subsequent chemotherapy or 6 weeks after the last protocol treatment. Severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). The WJOG Data and Safety Monitoring Committee reviewed serious adverse events for trial safety during the protocol treatment. Investigators assessed response, progression, and toxicities in their patients; independent central assessments of response and disease progression were not performed.

Statistical Analysis

The primary end point was OS, defined as time from random assignment to death resulting from any cause. Secondary end points were PFS, defined as time from random assignment to disease progression or death resulting from any cause; RR; toxicity; and proportion of patients who received subsequent chemotherapy.

Previous single-arm studies showed median OS of 5 and 6.9 months in paclitaxel-[15,16] and 8 and 10 months in irinotecan-containing regimen.[19,20] Irinotecan was contraindicated for patients with severe peritoneal metastasis, because its biliary-excreted metabolites caused severe toxicities. In gastric cancer, peritoneal metastasis often developed along with disease progression, and we therefore speculated that subsequent irinotecan after paclitaxel would be more difficult to apply in patients compared with the reverse treatment sequence. On the basis of these previous results and our assumption, this study was designed to detect 50% improvement in median OS from 5 months in the paclitaxel group to 7.5 months in the irinotecan group (hazard ratio [HR], 0.67). Assuming accrual and follow-up periods of 36 and 12 months, respectively, and using a two-sided log-rank test with 5% α and 20% β errors, 220 patients were required for the study. No interim analyses were planned.

A full analysis set (FAS) included all randomly assigned patients who met the eligibility criteria (patients found to be ineligible after random assignment were excluded). The safety analysis set (SAS) included all randomly assigned patients who received $\geq$ one dose of study medication. OS and PFS were analyzed in the FAS and estimated using the Kaplan-Meier method. RR was assessed in patients with $\geq$ one measurable lesion at baseline. Toxicity was analyzed in the SAS.

The primary analysis was planned for 1 year after enrollment of the last patient or approximately 205 events, whichever came first. An independent statistician and data analysis center performed the primary analysis for OS with unstratified log-rank test in the FAS population. All investigators remained blinded to the data until the analysis was completed. Cox proportional hazards models were used to calculate HRs and CIs. Fisher's exact test was used to assess differences in RR, incidence of

Table 1. Baseline Patient Demographic and Clinical Characteristics

Characteristic	Weekly Paclitaxel (n = 108) No.	%	Irinotecan (n = 111) No.	%
Sex				
Male	84	77.7	87	78.4
Female	24	22.2	24	21.6
Age, years				
Median	64.5		65	
Range	37-75		38-75	
ECOG PS				
0 to 1	104	96.3	107	96.4
2	4	3.7	4	3.6
Prior gastrectomy				
Yes	37	34.3	39	35.1
No	71	65.7	72	64.9
Prior chemotherapy				
S-1 plus cisplatin	92	85.2	102	91.9
Capecitabine plus cisplatin	13	12.4	8	7.2
S-1 plus oxaliplatin	3	2.8	1	0.9
Target lesion				
Yes	91	84.3	88	79.3
No	17	15.7	23	20.7
Histology				
Intestinal	54	50.0	54	48.6
Diffuse	54	50.0	57	51.4
Peritoneal metastasis				
Yes	28	25.9	28	25.2
No	80	74.1	83	74.8
No. of metastatic sites				
One	57	52.8	64	57.7
Two or more	51	47.2	47	42.3

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

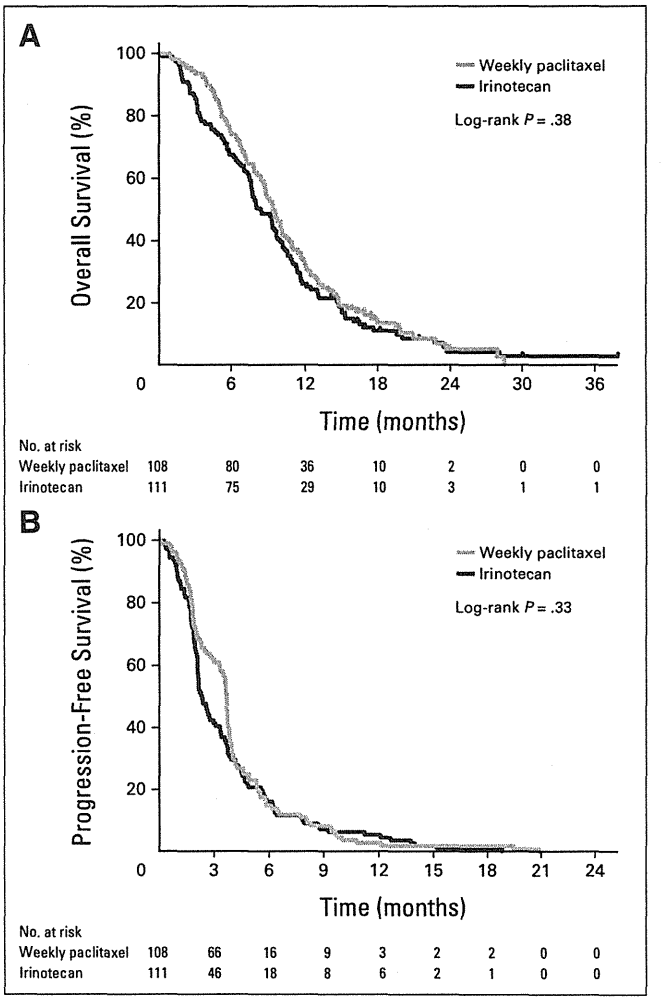

Fig 2. Kaplan-Meier curves of (A) overall and (B) progression-free survival.

adverse events, and proportion of patients who received third-line chemotherapy. Exploratory subgroup analyses of OS were performed using stratification and prognostic variables.

RESULTS

Patients

Between August 2007 and August 2010, 223 patients were enrolled from 37 centers in Japan. Of these patients, 111 were allocated to the paclitaxel group and 112 to the irinotecan group (Fig 1). Four patients, who either had received prior fluoropyrimidine monotherapy (paclitaxel group, n = 2; irinotecan group, n = 1) or had radiologically unconfirmed disease progression (paclitaxel group, n = 1), were ineligible for the study. Thus, the FAS consisted of 108 patients in the paclitaxel group and 111 patients in the irinotecan group. After random assignment, three patients in the paclitaxel group and two in the irinotecan group did not receive the protocol treatment. Thus, the SAS consisted of 108 patients in the paclitaxel group and 110 patients in the irinotecan group. Baseline characteristics of patients in the FAS were well balanced between the two treatment groups (Table 1). ECOG PS scores of 0 or 1 were found in a majority of patients. The most common first-line chemotherapy was S-1 plus cisplatin (88.6%), followed by capecitabine plus cisplatin with or without anti–epidermal growth factor receptor or anti–vascular endothelial growth factor antibodies (9.6%) and S-1 plus oxaliplatin (1.8%). One or more measurable lesions were present in approximately 80% of patients, and mild or moderate peritoneal metastasis was detected in approximately 25% of patients in both groups. Two or more metastatic sites were found in < 50% of patients.

Exposure to Chemotherapy

Median number of administrations was 11.5 (range, one to 46) in the paclitaxel group and 4.5 (range, one to 39) in the irinotecan group. Reasons for discontinuation of treatment included: disease progression (86.7%), adverse events (7.3%), withdrawal of consent (3.2%), and other reasons (2.8%). The proportion of patients in whom treatment was discontinued because of toxicity was 5.6% in the paclitaxel group and 9.1% in the irinotecan group.

Third-line chemotherapy was administered to 97 patients (89.8%) in the paclitaxel group and 80 patients (72.1%) in the irinotecan group ($P = .001$). In the paclitaxel group, third-line chemotherapy containing irinotecan was used in 81 patients (75.0%), and in the irinotecan group, a taxane-containing regimen was used in 67 patients (60.4%). Including later lines, 87 patients (80.6%) in the paclitaxel group received irinotecan, and 75 patients (67.6%) in the irinotecan group received paclitaxel.

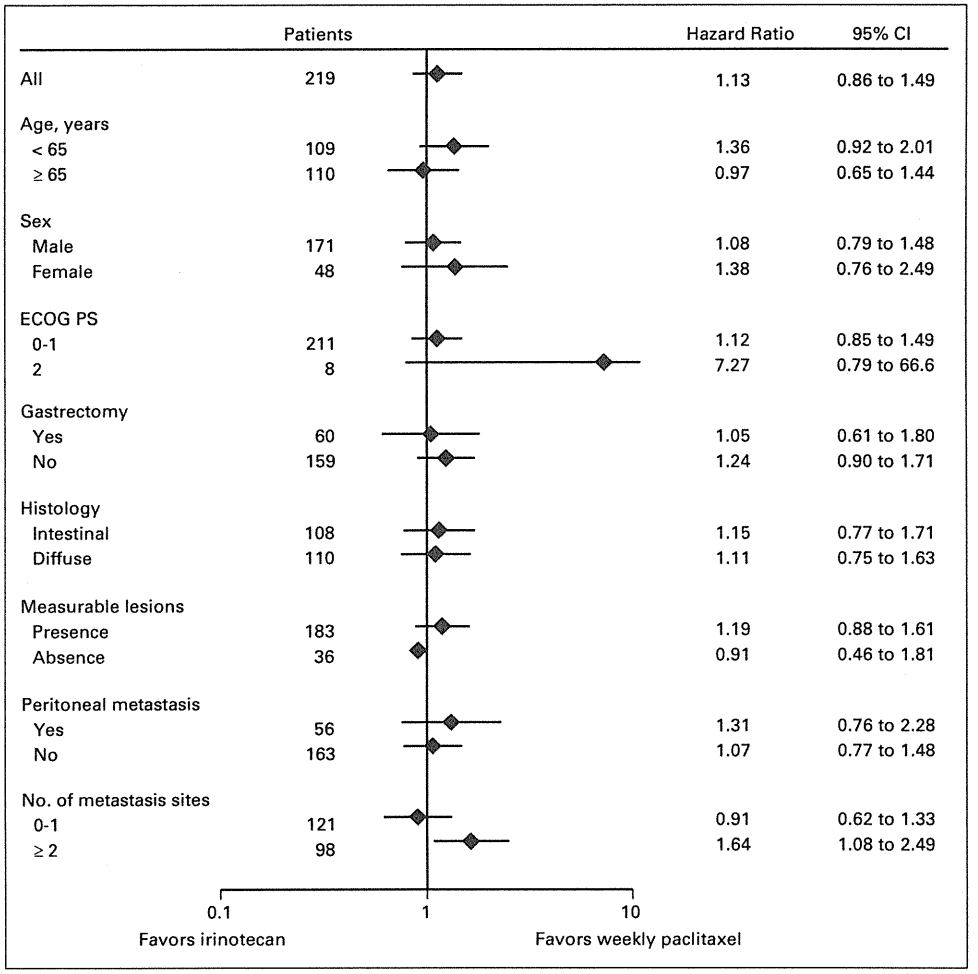

Fig 3. Forest plot of subgroup analyses. ECOG PS, Eastern Cooperative Oncology Group performance status.

Efficacy

In August 2011, after a median follow-up period of 17.6 months, 203 deaths (92.7%) were reported in the patient cohort. For the primary end point of OS, no statistically significant difference was observed between paclitaxel and irinotecan groups (HR, 1.13; 95% CI, 0.86 to 1.49; two-sided $P = .38$). Median OS was 9.5 months (95% CI, 8.4 to 10.7) in the paclitaxel group and 8.4 months (95% CI, 7.6 to 9.8) in the irinotecan group (Fig 2A). Median PFS was 3.6 months (95% CI, 3.3 to 3.8) in the paclitaxel group and 2.3 months (95% CI, 2.2 to 3.1) in the irinotecan group. This difference was not statistically significant (HR, 1.14; 95% CI, 0.88 to 1.49; two-sided $P = .33$; Fig 2B). RR was 20.9% (19 of 91 patients) in the paclitaxel group and 13.6% (12 of 88) in the irinotecan group (Fisher's exact $P = .24$).

Results of the subgroup analysis of OS are shown in Figure 3. Although treatment with weekly paclitaxel conferred a slight survival advantage in almost all subgroups, no significant interactions were observed in any subgroup. In an exploratory analysis, OS was analyzed in patients who received irinotecan and paclitaxel during second- and later-line chemotherapies. Median OS was 10.1 months in each group, and the survival curves of these two subgroups almost overlapped (HR, 0.96; 95% CI, 0.69 to 1.32; two-sided $P = .96$).

Safety

Table 2 lists adverse events and the proportion of patients experiencing adverse events during treatment in the SAS. The most common grade 3 or 4 adverse events were leukopenia (20.4%), neutropenia (28.7%), and anemia (21.3%) in the paclitaxel group. Leukopenia (19.1%), neutropenia (39.1%), anemia (30.0%), anorexia (17.3%), and hyponatremia (15.5%) were common in the irinotecan group. Grade 3 or 4 sensory neuropathy was observed in the paclitaxel group (7.4%) only. Grade 3 or 4 febrile neutropenia was more prevalent in the irinotecan group (9.1%) than in the paclitaxel group (2.8%). Three (2.7%) and four deaths (3.6%) resulting from any cause occurred within 30 days after the last administration in the paclitaxel and irinotecan groups, respectively. Treatment-related death confirmed by the independent data safety monitoring committee was observed in two patients (1.8%) in the irinotecan group. Causes of death included serious pneumonia in one patient and gastric perforation in the other.

Table 2. Adverse Events

	Weekly Paclitaxel (n = 108)				Irinotecan (n = 110)			
	All Grade		Grade 3 to 4		All Grade		Grade 3 to 4	
Adverse Event	No.	%	No.	%	No.	%	No.	%
Leukocytopenia	88	81.4	22	20.4	76	69.4	21	19.1
Neutropenia	85	78.7	31	28.7	77	70.0	43	39.1
Hemoglobin	69	63.9	23	21.3	84	76.4	33	30.0
Thrombocytopenia	6	5.6	1	0.9	15	13.6	2	1.8
Febrile neutropenia	3	2.8	3	2.8	10	9.1	10	9.1
Nausea	33	30.6	2	1.9	61	55.5	5	4.5
Vomiting	22	20.4	3	2.8	40	36.4	1	0.9
Anorexia	50	46.3	8	7.4	78	70.1	19	17.3
Diarrhea	21	19.4	1	0.9	49	44.5	5	4.5
Neuropathy (sensory)	62	57.4	8	7.4	2	1.8	0	0
Bilirubin	10	9.3	3	2.8	21	19.1	4	3.6
AST	32	29.6	4	3.7	42	38.2	9	8.2
ALT	24	22.2	3	2.8	41	37.3	3	2.7
Hyponatremia	21	19.4	4	3.7	35	31.8	17	15.5
Treatment-related death	0	0	0	0	2	1.8	2	1.8

DISCUSSION

To our knowledge, this was the first randomized phase III trial comparing paclitaxel and irinotecan in second-line chemotherapy for advanced gastric cancer. No statistically significant differences were observed between paclitaxel and irinotecan for the primary end point of OS or for other parameters evaluated in this study, including PFS and RR. Activity, feasibility, and tolerability of paclitaxel and irinotecan were comparable for second-line treatment of advanced gastric cancer.

When we planned this study, OS in patients who received second-line chemotherapy seemed to be longer than OS in patients who received BSC alone in previous trials.[12-16,19,20] Because > 70% of patients were receiving second-line chemotherapy as part of routine clinical practice at that time, conducting a trial of second-line chemotherapy compared with BSC alone was difficult in Japan. Since then, the survival benefit of second-line chemotherapy over BSC has been demonstrated in two randomized trials[22,23]: the AIO (Arbeitsgemeinschaft Internistische Onkologie) trial using irinotecan and Korean trial using irinotecan or docetaxel during the same time period as this WJOG 4007 study. On the basis of these results, second-line chemotherapy using irinotecan or docetaxel has been recognized as the standard of care for patients with gastric cancer. However, further comparison between irinotecan and taxane regimens would be valuable for strategic planning of treatment in patients with advanced gastric cancer.

In the Korean trial, choice of chemotherapy regimen—docetaxel or irinotecan—depended on investigator discretion. A subgroup analysis showed no significant difference in survival between regimens (median OS: docetaxel, 5.2 months *v* irinotecan, 6.6 months; $P = .116$).[23] In addition, Ji et al[24] conducted a retrospective analysis of 725 patients with gastric cancer treated with second-line chemotherapy; they found no relevant difference in OS between taxane and irinotecan treatment. In our exploratory subgroup analysis, no interaction was observed among several clinical factors; results favored neither paclitaxel nor irinotecan. Thus, either taxane or irinotecan can be recommended as a treatment option for second-line chemotherapy in patients with advanced gastric cancer.

Longer OS was achieved in this study than in previous phase III studies.[22,23] Many patients in good condition with small tumor burdens were enrolled onto our study. ECOG PS of 0 or 1 was recorded in almost all patients, and only one metastatic site was detected in > half of all patients. Additionally, excluding patients with severe peritoneal metastasis resulted in a lower proportion of patients (25.6%) with peritoneal metastasis, compared with those in the AIO (43%) and Korean (45%) trials.[22,23] These are well known as prognostic factors in advanced gastric cancer, and these patient-selection biases might have led to longer survival in our study.

In gastric cancer, peritoneal metastasis often develops along with disease progression, and irinotecan would be toxic for patients with

severe peritoneal metastasis. Indeed, the proportion of patients receiving subsequent irinotecan after second-line paclitaxel was only 24% in the previous report.[16] In this study, excluding patients with severe peritoneal metastasis seemed to result in a high proportion of patients (> 70%) receiving third-line chemotherapy, whereas 30% to 40% of patients did so in previous studies.[23,24] Although evidence is limited with regard to the efficacy of third-line chemotherapy in advanced gastric cancer, this therapy may have contributed to prolonged OS, and the unexpected higher proportion of those receiving third-line chemotherapy might have diluted a difference in OS between the paclitaxel and irinotecan groups.

Overall toxicity in both treatment arms was acceptable for second-line chemotherapy. In the paclitaxel group, common grade 3 or 4 toxicities (≥ 10%) included leukocytopenia, neutropenia, and anemia. Grade 3 sensory neuropathy, which was specific to paclitaxel, occurred at an incidence < 10% in this study. These toxicity profiles and severity levels are consistent with those in previous reports.[15,16] In the irinotecan group, leukocytopenia, neutropenia, anemia, anorexia, and hyponatremia were commonly observed. Frequency and severity of these toxicities were also consistent with those in previous reports.[22,23] Severe diarrhea, which is a well-known adverse reaction to irinotecan, generally occurs less frequently in Asian patients than in Western patients. In fact, grade 3 or 4 diarrhea was observed in 4.5% of patients in this trial, 8% of those in the Korean trial,[23] and 26% of those in the AIO trial.[22] Although ethnic diversity in metabolism of irinotecan has been suggested, the dosage of irinotecan is commonly higher in Western countries than in Asian countries. This may explain the different incidence of severe diarrhea between this and other studies.

Our study has several limitations. Participants were all Japanese; tumor biology may differ from that in Western patients.[25] In addition, a majority of patients received S-1 plus cisplatin as first-line chemotherapy, whereas S-1 is not popular in Western countries. However, a large, global phase III study (FLAGS [First-Line Therapy in Patients With Advanced Gastric Cancer Study] trial) demonstrated S-1 plus cisplatin to be similar in efficacy to fluorouracil plus cisplatin.[7] This difference in regimens used as first-line chemotherapy may have had little influence on interpretation of results of our study. Because patients with severe peritoneal metastasis were excluded from our study to avoid confounding effects of serious adverse events resulting from irinotecan, our results are not applicable to patients with severe peritoneal metastasis. Another trial is needed to determine the most appropriate treatment in such patients. As for statistical consideration, our hypothesis was 50% improvement in median OS in the irinotecan group over weekly paclitaxel group, and this resulted in a relatively small sample size. Therefore, if a small but true benefit existed in either group, this study may have been underpowered to detect it.

In conclusion, no difference in OS between paclitaxel and irinotecan groups was observed in this study. Both are considered reasonable second-line treatment options. The differences in toxicity profile and treatment schedule between both treatments will help in choosing either irinotecan or paclitaxel. Currently, several randomized trials investigating additional benefits of molecular targeting agents in second-line chemotherapy are planned or being conducted using weekly paclitaxel or irinotecan as a platform or reference regimen. The findings of our study are relevant to these future trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Postprogression survival for first-line chemotherapy of patients with advanced non-small-cell lung cancer

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Background: Given the growing number of drugs available for non-small-cell lung cancer (NSCLC), an effect of first-line chemotherapy on overall survival (OS) might be confounded by subsequent therapies. We examined the relation between postprogression survival (PPS) and OS in phase III trials of first-line chemotherapy for advanced NSCLC.
Patients and methods: A literature search identified 69 trials that were published during the past decade. We partitioned OS into progression-free survival (PFS) and PPS and evaluated the relation between OS and either PFS or PPS. We also examined whether any association might be affected by the year of completion of trial enrollment.
Results: The average PPS was longer in recent trials than in older trials (6.5 versus 4.4 months, $P < 0.0001$). For all trials, PPS was strongly associated with OS ($r = 0.82$), whereas PFS was moderately associated with OS ($r = 0.43$). The correlation between OS and PPS in recent trials was stronger than that in older trials ($r = 0.89$ and 0.66).
Conclusions: Our findings indicate that, especially for recent trials, PPS is highly associated with OS in first-line chemotherapy for advanced NSCLC, whereas PFS is only moderately associated with OS.
Key words: chemotherapy, non-small-cell lung cancer, overall survival, phase III trial, progression-free survival

introduction

Lung cancer remains the leading cause of cancer death worldwide [1, 2], with non-small-cell lung cancer (NSCLC) accounting for ~85% of lung cancer cases. Most individuals with NSCLC have metastatic disease at the time of diagnosis and therefore have a poor prognosis. The standard treatment of advanced NSCLC over the past decade has been platinum-based chemotherapy because of the moderate improvement in survival it confers [3–6]. Although many patients initially achieve clinical remission or disease stabilization with first-line chemotherapy, nearly all subsequently experience disease progression and eventually die of advanced NSCLC.

Overall survival (OS) has been traditionally recognized as the most important therapeutic objective for NSCLC patients. However, in view of the growing number of drugs and combinations thereof that are available for the treatment of such patients, any effect of first-line chemotherapy on OS might be confounded by subsequent therapies [7]. Indeed, an improvement in progression-free survival (PFS) has not necessarily resulted in an improved OS in recent randomized trials in patients with NSCLC [8, 9].

The effect of therapies instituted after disease progression on survival in clinical trials is thus of interest. However, little is known about postprogression survival (PPS) in NSCLC. In the present study, we partitioned OS of phase III trials for chemotherapy-naive patients with NSCLC into PFS and PPS and assessed the association of each with OS.

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methods

search strategy and selection of trials

An independent review of PubMed citations from 1 January 2000 to 31 October 2010 was carried out. Key words included in the search were 'non–small cell lung cancer', 'clinical trial', 'advanced', and 'chemotherapy'. The search was limited to randomized controlled phase III trials and articles published in English. We reviewed each publication, and phase III studies that compared two or more first-line systemic chemotherapies (including treatment with molecularly targeted agents) for advanced or metastatic NSCLC were selected. To find any additional trials, we searched the reference lists of included trials as well as of large systematic reviews. We also checked articles that were in press at leading journals and searched websites listing abstracts from conferences (organized by the American Society of Clinical Oncology or the Federation of European Cancer Societies). We included trials that provided data for both OS and either PFS or time to progression (TTP), whether or not these parameters were explicitly defined. Trials were excluded if they investigated only immunotherapy regimens or hormonal therapies. Trials that were designed to assess combined modality treatments, including radiation therapy and surgery, were also excluded. To avoid bias, two observers (HH and IO) independently abstracted the data from the trials.

data abstraction

We analyzed in detail the primary and secondary efficacy end points, following the definitions of the authors of each trial. When not specifically

stated by the authors, we considered the primary end point to be that used for calculation of sample size. For the sake of simplicity, two end points (PFS and TTP) based on tumor assessment are collectively referred to as PFS in the present study, similar to the approach adopted in a recent report [10]. Median OS and median PFS were extracted from all trials that provided data for each treatment group. Median PPS was defined as median OS minus median PFS for each trial. We also obtained the following information from each report: year of completion of trial enrollment, number of patients randomized, number of patients in each treatment arm, number of treatment arms in each trial, proportion of patients who were male or had adenocarcinoma, and median age of the patients.

data analysis

We summarized the survival data (median OS, median PFS, median PPS, and median PFS/median OS) as the average and standard error (SE) for trial arms. SE was calculated on the basis of previously described models [11]. We also calculated the percentage of OS accounted for by PPS for each trial arm as: 100 − (100 × median PFS/median OS). To assess the relation between median OS and either median PFS or median PPS, we used Spearman's rank correlation coefficient. To account for differences in sample size among trial arms, we weighted all analyses by the number of patients in each arm. In addition, all trials were divided into two groups on the basis of the year in which trial enrollment was completed. Given that the median year for completion of enrollment in the 69 analyzed trials was 2002, we dichotomized at year 2002 (older trials, up to and including 2002; recent trials, 2003 and later) in order to evaluate a possible change in PPS, and we assessed whether the evaluated relations might be dependent on the year of completion of trial enrollment. We examined differences in the survival data between older and recent trials by normal approximation of the average survival data (z test). All reported P-values correspond to two-sided tests, and those of P-values <0.05 were considered statistically significant. Analyses were carried out with SAS for Windows release 9.2 (SAS Institute, Cary, NC).

results

characteristics of the trials

Our search yielded a total of 467 potentially relevant publications. Initially, 366 studies were excluded for at least one of the following reasons: they examined other malignancies or combined modality treatments, they were not randomized, they were phase I or II trials, they were review articles, they represented subgroup analyses, or they were duplicates. The selection process for the randomized controlled trials is shown in Figure 1. Review of the remaining 101 publications yielded 69 trials that were considered to be highly relevant for the present study. The main characteristics of the 69 phase III trials included in the analysis are listed in Table 1. A total of 37 986 patients with advanced NSCLC were enrolled, with a median number of patients per study of 433 (range 153–1725). Most of the trials had a high proportion of male patients and of patients with adenocarcinoma. The average median age of the patients was 62.3 years. Ten trials used an end point based on tumor assessment (PFS or TTP) as the primary end point, whereas OS was assessed as the primary end point in 53 trials. The other six trials used response rate or quality of life as the primary end point.

median OS, PFS, and PPS in all trials and in subgroups based on year of completion of trial enrollment

The survival data for trial arms according to the year in which trial enrollment was completed are shown in Table 2. Although the average median PFS in older (up to and including 2002) trials was the same (4.9 months) as that in recent (2003 and later) trials, the average median PPS was ~50% longer in the

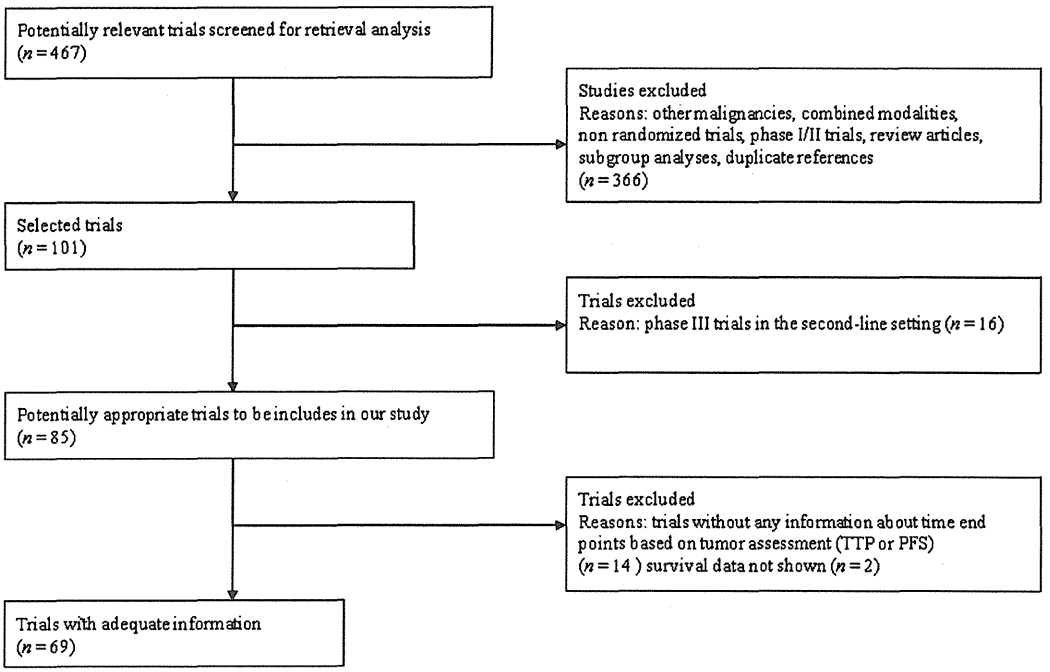

Figure 1. Flow chart showing the progress of trials through the selection process.

recent trials than in the older trials (6.5 and 4.4 months, respectively, $P < 0.0001$). The average proportion of median OS accounted for by median PPS significantly increased from 45.9% in older trials to 54.9% in recent trials ($P < 0.0001$).

relation between OS and either PFS or PPS

The relation between median OS and either median PFS or median PPS for the 151 treatment arms of the 69 trials is shown in Figures 2 and 3, respectively. We found that median PPS was strongly associated with median OS ($r = 0.82$, $P < 0.0001$) on the basis of Spearman's correlation coefficient, whereas median PFS was more moderately correlated with median OS ($r = 0.43$, $P < 0.0001$). The association between median OS and median PPS in recent trials ($r = 0.89$, $P < 0.0001$) was stronger than that in older trials ($r = 0.66$, $P < 0.0001$), whereas the correlation between median OS and median PFS in recent trials ($r = 0.55$, $P < 0.0001$) was similar to that in older trials ($r = 0.44$, $P < 0.0001$).

Table 1. Characteristics of the 69 phase III trials for advanced non-small-cell lung cancer included in the present analysis

Trial characteristics	
Median no. of patients per trial (range)	433 (153–1725)
Percentage of male patients (median)[a]	70.2
Percentage of adenocarcinoma patients[b]	51.2
Average of median age (years)[c]	62.3
Primary end point (no. of trials)	
OS	53
PFS or TTP	10
Response rate	3
Quality of life or toxicity	3
End point based on tumor assessment	
TTP	39
PFS	30
No. of treatment arms	
2	58
3	9
4	2

[a]One trial was excluded (data were not shown).
[b]Five trials were excluded (data were not shown).
[c]One trial was excluded (data were not shown).
OS, overall survival; PFS, progression-free survival; TTP, time to progression.

discussion

In the present study, we defined median PPS as median OS minus median PFS for each treatment arm of phase III trials for chemotherapy-naive patients with advanced NSCLC, as previously described [10, 12]. We also investigated the relation between median OS and either median PPS or median PFS by correlation analysis and found that median OS was more strongly associated with median PPS than with median PFS. Moreover, we also found that the correlation between median PPS and median OS was more pronounced in recent trials than in older trials and that median PPS was longer in recent trials than in older trials. This recent prolongation of PPS is likely the result of the increasing number of active compounds, such as docetaxel, pemetrexed, and epidermal growth factor receptor–tyrosine kinase inhibitors (EGFR-TKIs), which are available for second- or third-line chemotherapy in advanced NSCLC. One trial from a decade ago, when pemetrexed and EGFR-TKIs were not available, reported that only ~20% of patients received second-line chemotherapy [13]. In contrast, in the AVAiL trial, a recent large phase III trial that investigated the efficacy of cisplatin–gemcitabine with or without bevacizumab, second-line chemotherapy was administered in >60% of patients [8, 9]. Clinical trials of chemotherapy for patients with refractory NSCLC yielded a median OS of 5–8 months [14–17], which is similar to the median PPS for recent trials in our analysis. The recent widespread use of active second- and third-line therapies thus appears to have contributed to a prolongation of PPS in patients with advanced NSCLC.

Broglio and Berry [12] recently focused on PPS, which they termed survival postprogression (SPP) and defined as OS minus PFS, in a hypothetical clinical trial setting under the assumption that there was a treatment difference in PFS but not in PPS [12]. As the median PPS increased, the probability of detecting a statistically significant difference in OS decreased substantially. Even for a trial with an observed P value for improvement in PFS of 0.001, whereas there was a >90% probability for statistical significance of the difference in OS if the median PPS was 2 months, this probability decreased to only ~50% if the median PPS was 6 months. In the present study, we found that median PPS constituted more than half of median OS and that median PPS was >6 months in recent trials for NSCLC.

Table 2. Average median PFS, OS, and PPS as well as the average proportion of OS accounted for by PPS for trial arms in all trials or in trials according to year of completion of trial enrollment

Trials	No. of arms	No. of patients	Average median (months)			Average PPS/OS (%)
			PFS	OS	PPS	
All	151	37 986	4.9 (0.09)	10.3 (0.24)	5.4 (0.22)	50.1 (1.00)
Recent (2003 and later)	69	19 334	4.9 (0.13)	11.3 (0.42)	6.5 (0.37)	54.9 (1.31)
Older (up to and including 2002)	82	18 652	4.9 (0.13)	9.4[a] (0.17)	4.4[a] (0.16)	45.9[a] (1.33)

Values in brackets are standard errors.
[a]$P < 0.0001$ versus the corresponding value for recent trials (z test).
OS, overall survival; PFS, progression-free survival; PPS, postprogression survival; TTP, time to progression.

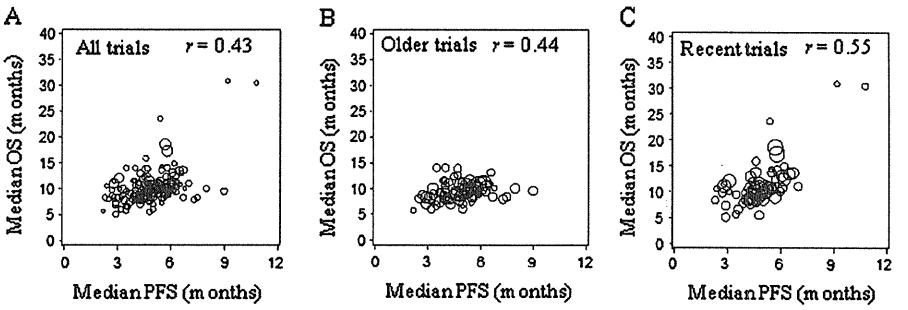

Figure 2. Relation between median overall survival (OS) and median progression-free survival (PFS) for 151 arms of 69 phase III trials for advanced non-small-cell lung cancer. (A) All trials. (B) Older trials (trial enrollment finished between 1996 and 2002). (C) Recent trials (trial enrollment finished between 2003 and 2006). The area of each circle is proportional to the number of patients in each trial arm. The *r* values represent Spearman's rank correlation coefficient.

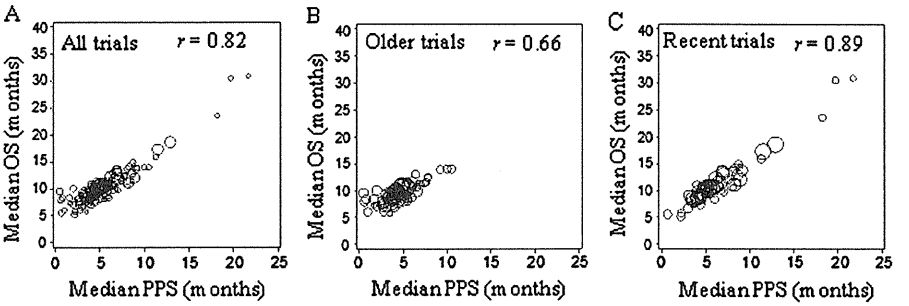

Figure 3. Relation between median overall survival (OS) and median progression-free survival (PPS) for 151 arms of 69 phase III trials for advanced non-small-cell lung cancer. (A) All trials. (B) Older trials (trial enrollment finished between 1996 and 2002). (C) Recent trials (trial enrollment finished between 2003 and 2006). The area of each circle is proportional to the number of patients in each trial arm. The *r* values represent Spearman's rank correlation coefficient.

Surrogacy of PFS for OS has often been assessed by quantifying the strength of the association between these end points at the individual level (referred to as individual-level surrogacy) and of that between the effects of treatment on these end points (trial-level surrogacy) [18–21]. Our examination of the correlation between PFS and OS was not an exercise in surrogate validation because of the lack of investigation into the correlation between the effects of chemotherapy on these end points. However, the present study has yielded the key finding that PPS, not PFS, is highly associated with OS.

The present study has several limitations. First, our analysis was based on abstracted data. The use of individual patient data might be expected to allow a better characterization of the relation between OS and other end points based on tumor assessment, including PFS and TTP. However, such an approach would restrict the analysis to a small number of trials and would hinder its replication by independent researchers. Second, the results of our study potentially have several confounders due to selection of many heterogeneous trials for analysis. The results are generally unaccountable without appropriate adjustment for patient characteristics dependent on differences in predefined eligibility criteria for enrollment in the clinical trials. Third, the assessment of disease progression is potentially subject to measurement error and bias in individual patients, and the quality of measurement for end points based on tumor assessment can vary between centers and trials. Finally, two end points (PFS and TTP) based on tumor assessment are considered as the same parameter, following the example of a previous report for advanced breast cancer [10]. PFS is defined as the time from randomization to tumor progression or death, whereas TTP is defined similarly but considers death as a time point when censoring occurs. TTP is the same as PFS if death does not occur during treatment. Given that death rarely occurs before disease progression in advanced NSCLC, we reasonably considered PFS to be the same as TTP for our analysis. Indeed, we separately analyzed clinical trials providing PFS (n = 63 arms) or TTP (n = 88 arms), and we found a consistent association between OS and PPS (data not shown). These data thus support our approach in which these two end points (PFS and TTP) are collectively referred to as PFS in the present analysis.

As far as we are aware, our study is the first to analyze PPS in advanced NSCLC. Our findings indicate that, especially for recent trials, PPS is highly associated with OS for first-line chemotherapy in patients with advanced NSCLC, whereas PFS is only moderately associated with OS. Therefore, OS remains an appropriate end point of clinical trials for chemotherapy-naive patients with advanced NSCLC. Given the great effect of PPS on OS, we propose a precise assessment of clinical course after disease progression in each clinical trial.

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disclosure

The authors declare no conflicts of interest.

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