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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

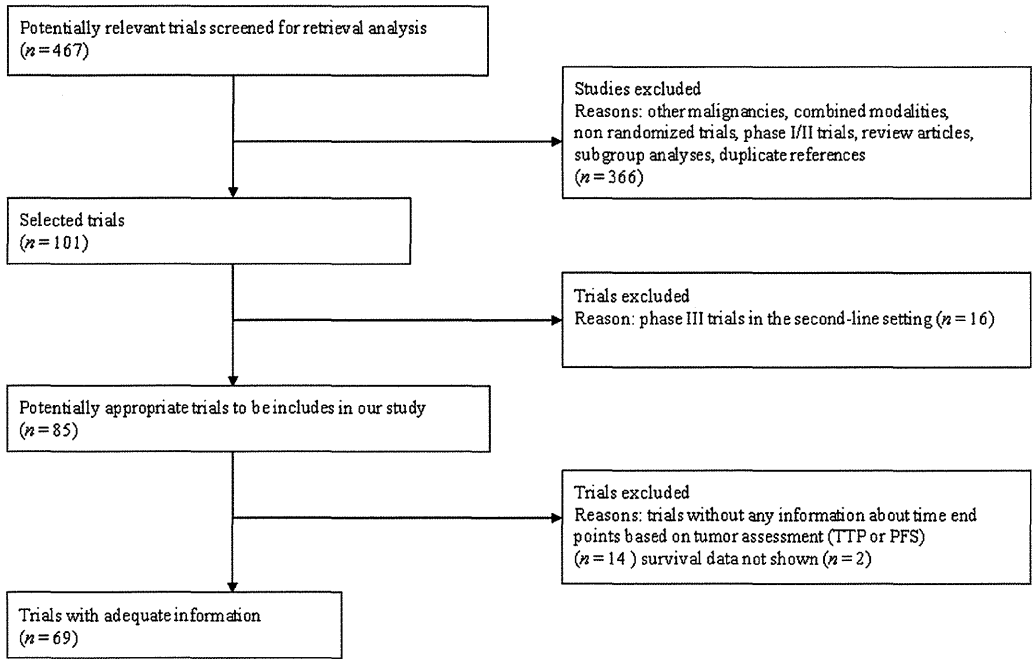


**Figure 1.** Flow chart showing the progress of trials through the selection process.

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.

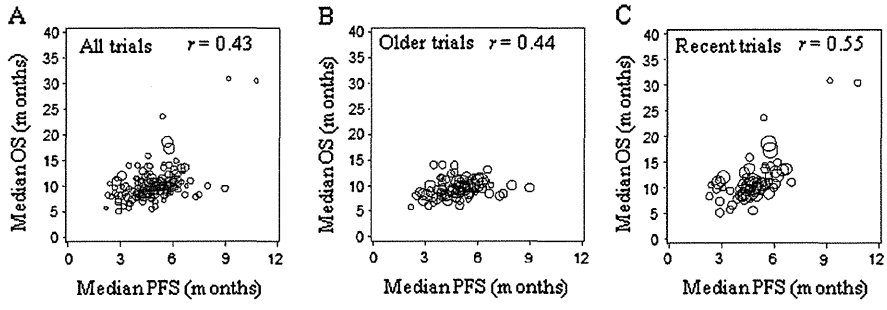


**Figure 2.** Relation between median overall survival (OS) and median progression-free survival (PFS) for 151 arms of 69 phase III trials for advanced non-small-cell lung cancer. (A) All trials. (B) Older trials (trial enrollment finished between 1996 and 2002). (C) Recent trials (trial enrollment finished 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.

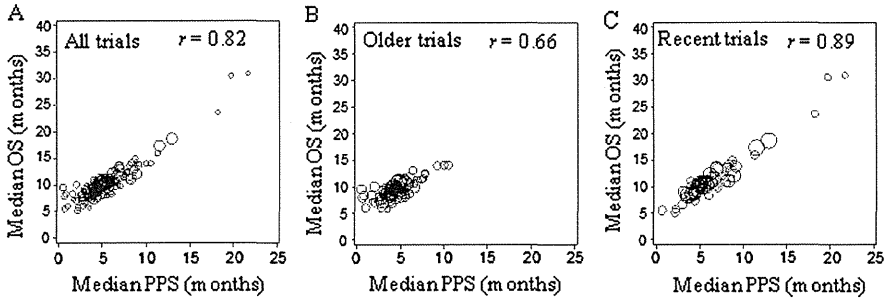


**Figure 3.** Relation between median overall survival (OS) and median progression-free survival (PPS) for 151 arms of 69 phase III trials for advanced non-small-cell lung cancer. (A) All trials. (B) Older trials (trial enrollment finished between 1996 and 2002). (C) Recent trials (trial enrollment finished 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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# Use of $^{11}$C-methionine PET parametric response map for monitoring WT1 immunotherapy response in recurrent malignant glioma

## Clinical article

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*Object.* Immunotherapy targeting the *Wilms tumor 1 (WT1)* gene product is a promising treatment modality for patients with malignant gliomas, and there have been reports of encouraging results. It has become clear, however, that Gd-enhanced MR imaging does not reflect prognosis, thereby necessitating a more robust imaging evaluation system for monitoring response to WT1 immunotherapy. To meet this demand, the authors performed a voxel-wise parametric response map (PRM) analysis of $^{11}$C-methionine PET (MET-PET) in WT1 immunotherapy and compared the data with the overall survival after initiation of WT1 immunotherapy ($OS_{WT1}$).

*Methods.* Fourteen patients with recurrent malignant glioma were included in the study, and $OS_{WT1}$ was compared with: 1) volume and length change in the contrast area of the tumor on Gd-enhanced MR images; 2) change in maximum uptake of $^{11}$C-methionine; and 3) a more detailed voxel-wise PRM analysis of MET-PET pre- and post-WT1 immunotherapy.

*Results.* The PRM analysis was able to identify the following 3 areas within the tumor core: 1) area with no change in $^{11}$C-methionine uptake pre- and posttreatment; 2) area with increased $^{11}$C-methionine uptake posttreatment ($PRM^{+MET}$); and 3) area with decreased $^{11}$C-methionine uptake posttreatment. While the results of Gd-enhanced MR imaging volumetric and conventional MET-PET analysis did not correlate with $OS_{WT1}$ ($p = 0.270$ for Gd-enhanced MR imaging length, $p = 0.960$ for Gd-enhanced MR imaging volume, and $p = 0.110$ for MET-PET), the percentage of $PRM^{+MET}$ area showed excellent correlation ($p = 0.008$) with $OS_{WT1}$.

*Conclusions.* This study describes the limited value of Gd-enhanced MR imaging and highlights the potential of voxel-wise PRM analysis of MET-PET for monitoring treatment response in immunotherapy for malignant gliomas. Clinical trial registration no.: UMIN000002001.
*(http://thejns.org/doi/abs/10.3171/2011.12.JNS111255)*

**Key Words • glioma • $^{11}$C-methionine PET • WT1 immunotherapy • parametric response map • oncology**

Malignant glioma remains a devastating intracranial neoplasm. In particular, patients with newly diagnosed GBM have a median overall survival of only 14.6 months, even when treated with chemotherapeutic agents such as temozolomide.[17] On the other hand, the products of the *WT1* gene have been shown to be overexpressed in malignant gliomas,[12,13] and this makes the WT1 antigen an attractive target for immunotherapy against malignant glioma.

The results of WT1 immunotherapy have been previously reported for the initial 21 patients participating in an ongoing Phase II clinical trial of WT1 vaccination for patients with recurrent malignant glioma, and the safety and efficacy of WT1 vaccination have been described (Phase I/II clinical trial of WT1 peptide-based vaccine for the patients with malignant tumors. UMIN000002001).[9]

*Abbreviations used in this paper:* GBM = glioblastoma multiforme; MET-PET = $^{11}$C-methionine PET; $OS_{WT1}$ = overall survival after initiation of Wilms tumor 1 immunotherapy; PRM = parametric response map; RECIST = Response Evaluation Criteria in Solid Tumors; ROI = region of interest; WT1 = Wilms tumor 1.

This article contains some figures that are displayed in color online but in black and white in the print edition.

The median overall survival time after initiating WT1 immunotherapy was 36.7 weeks. In that report, the antitumor effect of the treatment was assessed by determining the response of the target lesions using MR imaging 12 weeks after initiating WT1 vaccination. The tumor length, corresponding to the contrast-enhanced area on Gd-enhanced MR images, was measured and analyzed according to RECIST version 1.0,[18] with results reported as complete response, partial response, stable disease, and progressive disease.

In that analysis, however, the long-term survivors were assessed as having progressive disease at 12 weeks after WT1 vaccination initiation, suggesting that evaluation by contrast-enhanced T1-weighted MR imaging is not suitable for assessing the treatment response to WT1 immunotherapy. The fact that morphological imaging often does not adequately reflect the underlying tumor biology[3] imposes a considerable demand to develop alternative biological markers for therapeutic response. Recently, a voxel-wise PRM has been developed to overcome the above-mentioned issue in other treatment modalities for malignant glioma.[6–8]

The present report focuses on the results in 14 patients who were enrolled in the same trial but were not included in the previous report. In this study, we have attempted to apply the voxel-wise PRM method to MET-PET in the setting of WT1 immunotherapy against recurrent malignant glioma and compare its clinical value with conventional analytical methods based on MR imaging and PET.

## Methods

### *WT1 Immunotherapy*

Patients received intradermal injections of 3.0 mg of modified 9-mer WT1 peptide emulsified with Montanide ISA51 adjuvant. The WT1 vaccinations were given weekly for 12 consecutive weeks. Twelve weeks after the initial vaccination, the response was evaluated by means of both MR imaging and MET-PET. Our local internal review board approved this treatment and written informed consent was obtained from all patients. Details of the procedures and protocol have been reported elsewhere.[9,14]

### *Patient Selection*

Between 2004 and 2010, 66 patients with recurrent malignant glioma were treated with WT1 immunotherapy as described above as part of an ongoing clinical trial (UMIN000002001). Nineteen of these 66 patients underwent evaluation by means of MET-PET. These patients were not included in our previous report.[9] Five of these 19 patients—2 patients with intratumoral hematoma and 3 patients whose tumor volume was 2 $cm^3$ or less as measured by MET-PET—were excluded from the current analysis. All 14 patients whose data were analyzed for this study underwent MR imaging and MET-PET before (pre-WT1) and 12 weeks after (post-WT1) WT1 vaccination. Detailed information pertaining to these 14 patients is listed in Table 1. The overall survival was measured from WT1 immunotherapy initiation, denoted as $OS_{WT1}$.

### *Magnetic Resonance Imaging*

All MR images were obtained using a 3.0-T whole-body MR scanner (Signa, GE Medical Systems) with an acquisition time of approximately 3 minutes. After intravenous administration of Gd–diethylenetriamine pentaacetic acid (Gd-DTPA; 0.1 mmol/kg body weight), axial T1-weighted images were obtained using standard procedures. Those images were stored in 512 × 512 × 23 or 216 anisotropic voxels, with each voxel being 0.43 × 0.43 × 6.0 or 1.0 mm.

### *MET-PET Scans*

All PET studies were performed using the Eminence PET system (Shimadzu Corp.). $^{11}$C-methionine (111–222 MBq, 3–6 mCi), synthesized according to the method of Berger et al.,[1] was injected intravenously. Tracer accumulation was recorded over 15 minutes in 99 transaxial slices from the entire brain. Total activity from 20 to 35 minutes after tracer injection was used for image reconstruction. The images were stored in 256 × 256 × 99 anisotropic voxels, with each voxel being 1 × 1 × 2.6 mm.

### *Tumor Length and Volume Measurement*

Tumor length, corresponding to the contrast-enhanced area on T1-weighted MR images, was measured and analyzed according to RECIST version 1.0,[18] using the ImageJ software from the National Institutes of Health (http://rsb.info.nih.gov/ij/).

Tumor volume was measured by performing a 3D threshold-based volume-of-interest analysis in all patients for contrast-enhanced lesions on Gd-enhanced MR images, using the ImageJ software. The contrast-enhanced area in each slice image was measured by manual tracking of the tumor boundaries, and the sum of the enhanced areas or high-uptake areas was multiplied by the slice interval.

### *Image Fusion and Registration*

The MET-PET data were registered onto pre-WT1 contrast-enhanced T1-weighted standard anatomical images using normalized mutual information with the VINCI image analyzing software from the Max Planck Institute for Neurological Research in Cologne (http://www.nf.mpg.de/vinci/). Registration of the images was confirmed visually. The reported registration error for normalized mutual information is less than 1 mm.[19] After image registration was completed, all image sets, including the standard anatomical MR images (pre-WT1) and MET-PET data (pre- and post-WT1), were converted into 256 × 256 × 256 isotropic, 1 × 1 × 1 mm images enabling further voxel-wise analysis of the images (Fig. 1).

### *Data Processing and ROI Selection*

Three data sets (standard anatomical images and MET-PET data) were exported to in-house software written in MATLAB 7.6 (MathWorks) for further analysis. Regions of interest were selected as follows: for normal brain tissue, the contralateral hemisphere of the tumor was selected, including both the gray and white matter; for tumor, contrast-enhanced lesions were selected.

**TABLE 1: Summary of clinical and demographic characteristics of 14 patients***

| Case No. | Age (yrs),† Sex | ECOG PS | Diagnosis | Response per RECIST | $OS_{WT1}$ (wks)‡ | Tumor Vol by MET-PET ($cm^3$)§ |
|---|---|---|---|---|---|---|
| 1 | 43, M | 2 | GBM | SD | 87.1 | 31.2 |
| 2 | 64, M | 1 | GBM | PD | 144.7 | 63.8 |
| 3 | 76, M | 1 | GBM | SD | 144.6 | 29 |
| 4 | 60, F | 0 | GBM | SD | 61.7 | 58.1 |
| 5 | 20, F | 0 | GBM | PR | 29.3 | 24.9 |
| 6 | 64, F | 1 | AA | SD | 65.0 | 51 |
| 7 | 29, M | 2 | GBM | PD | 20.9 | 15.4 |
| 8 | 28, M | 1 | GBM | SD | 57.7 | 9 |
| 9¶ | 62, M | 0 | gliosarcoma | SD | 77.0 | 11.5 |
| 10 | 36, F | 1 | AA | SD | 60.3 | 3.8 |
| 11 | 44, M | 0 | GBM | PD | 48.1 | 13.2 |
| 12 | 62, F | 1 | GBM | PD | 18.7 | 5 |
| 13 | 51, M | 0 | GBM | PD | 35.0 | 39.3 |
| 14 | 39, F | 1 | GBM | PD | 27.6 | 15.2 |

* AA = anaplastic astrocytoma; ECOG PS = Eastern Cooperative Oncology Group Performance Status; PD = progressive disease; PR = partial response; SD = stable disease.

† Mean 48.4 years.

‡ Median 59.0 weeks.

§ Median 26.5 $cm^3$.

¶ The patient in Case 9 was alive as of this writing.

*Parametric Response Map Calculation Algorithm*

As in Fig. 1, post-WT1 $^{11}$C-methionine uptake was plotted as a function of pre-WT1 $^{11}$C-methionine uptake in both normal brain and Gd-enhancing lesions. A linear regression fitting was applied to the data obtained by the ROI placed at the normal brain (Fig. 1, *blue line*), which can be expressed as follows: post-WT1 MET-PET = pre-WT1 MET-PET, where "post-WT1 MET-PET" and "pre-WT1 MET-PET" are the tumor/normal tissue (T/N) ratio of pre- and post-WT1 $^{11}$C-methionine PET.

Next, the magnitude of deviation of each data point *(i)* from the expected linear regression fitting was calculated as follows:

$$\text{deviation}_i = [(\text{post-WT1 MET-PET})_i - (\text{pre-WT1 MET-PET})_i] / \sqrt{2}$$

The parametric response map (PRM) of each data point was defined as follows:

$$PRM_i = \text{deviation}_i - \mu / \rho$$

where $\mu$ and $\rho$ are the mean and standard deviation of $\text{deviation}_i$ within the ROI placed at the normal brain. In other words, PRM is identical to the z-score of each data point in the lesion from the expected linear regression line calculated for normal brain.

*Statistical Analysis*

Statistical analyses were carried out using a Kaplan-Meyer survival analysis with the log-rank test if not specified otherwise. A p value < 0.05 was considered statistically significant, and all statistical computation was performed using Prism 5 (GraphPad Software, Inc.) or JMP 9.0 (SAS Institute, Inc.).

## Results

*Applying the PRM Calculation to WT1 Immunotherapy Patients*

The PRM calculation, described above and in Fig. 1, was successfully performed in all 14 cases. The actual process that was performed is described below by presenting 2 representative cases, one (Case 2) in which the patient had a relatively long $OS_{WT1}$ of 144.7 weeks and was considered a treatment responder, and another (Case 7) in which the patient had a relatively short $OS_{WT1}$ of 20.9 weeks and was considered a treatment nonresponder.

*Representative Treatment Responder.* A representative case involving a treatment responder (Case 2) is illustrated in Fig. 2. First, a voxel-wise analysis was performed in normal brain tissue (Figs. 1 and 2). As shown in Fig. 2, pre- and post-WT1 $^{11}$C-methionine uptake showed good positive linear correlation in normal brain tissue. A linear regression line and the ± 2 SD distribution range were calculated. Subsequently, the same analysis was performed in a tumor lesion. A contrast-enhanced area was selected as the ROI for analysis. In this particular case, most voxels were distributed in the –2 SD area, suggesting that $^{11}$C-methionine uptake decreased after WT1 immunotherapy (Fig. 2). This area is presented as $PRM^{-MET}$ (PRM with reduced methionine uptake).

This patient survived for 144.7 weeks after initiation of WT1 immunotherapy, although the contrast-enhanced area increased after WT1 immunotherapy, categorizing this patient as having progressive disease in the Gd-enhanced MR imaging–based RECIST analysis.

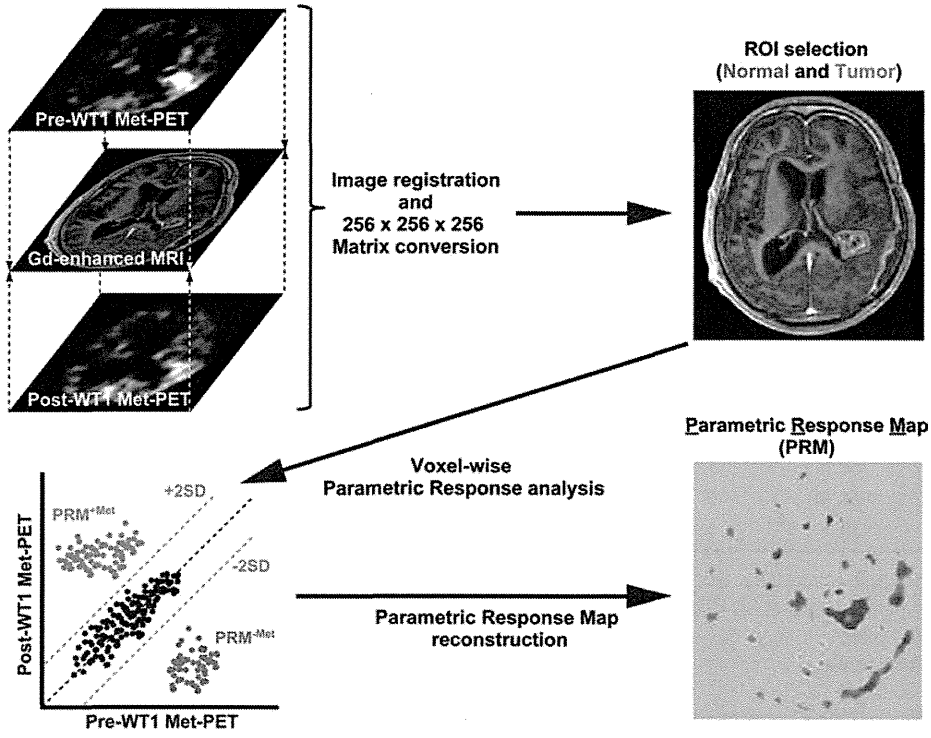


**Fig. 1.** Image processing procedures. $^{11}$C-methionine PET data obtained before and 12 weeks after WT1 immunotherapy initiation were fused and registered onto conventional contrast-enhanced MR images. All 3 images were converted into a 256 × 256 × 256, 1-mm isotropic image matrix. Post-WT1 $^{11}$C-methionine uptake was plotted as a function of pre-WT1 $^{11}$C-methionine uptake. After calculating the linear regression line with the ± 2 SD distribution range in contralateral normal brain tissue, an ROI was set at the contrast-enhanced pre-WT1 immunotherapy lesion. The obtained plots were categorized into the following 3 areas: 1) area of no change in $^{11}$C-methionine uptake pre- and posttreatment, 2) area with increased $^{11}$C-methionine uptake posttreatment ($PRM^{+MET}$), and 3) area with decreased $^{11}$C-methionine uptake posttreatment ($PRM^{-MET}$). These areas were reconstructed in images for visual inspection ($PRM^{+MET}$ in *red* and $PRM^{-MET}$ in *blue*).

*Representative Treatment Nonresponder.* A representative case in which the patient had only a short $OS_{WT1}$ (Case 7) is illustrated in Fig. 3. The same analysis as described above was performed. In this particular case, most voxels were distributed in the +2 SD area (PRM with increased methionine uptake [$PRM^{+MET}$]), suggesting that $^{11}$C-methionine uptake increased after WT1 immunotherapy. This patient survived for 20.9 weeks after initiation of WT1 immunotherapy.

### *Correlation of Treatment Response Assessment and $OS_{WT1}$*

*Magnetic Resonance Imaging–Based Assessment.* To assess the validity of evaluating the response to WT1 immunotherapy using contrast-enhanced MR imaging, the changes in length and volume of the tumor before and 12 weeks after initiating WT1 immunotherapy were calculated. As in Fig. 4A and B, both methods using Gd-enhanced MR imaging failed to show positive correlation with $OS_{WT1}$ ($p = 0.270$ and 0.960, respectively).

*Conventional MET-PET Analysis.* To assess the validity of evaluating the response to WT1 immunotherapy using MET-PET, the changes in maximum $^{11}$C-methionine uptake assessed using the tumor/normal tissue ratio (T/N max) before and 12 weeks after initiating WT1 immunotherapy were calculated. Change of T/N max failed to show any statistically significant correlation with $OS_{WT1}$ ($p = 0.110$) (Fig. 4C).

*Parametric Response Map Analysis.* Finally, correlation of the proposed voxel-wise PRM of MET-PET with $OS_{WT1}$ was investigated. Each voxel of contrast-enhanced area on the pretreatment MR images was categorized as a no-change area, $PRM^{+MET}$, or $PRM^{-MET}$, according to no change, increase, or decrease, respectively, in methionine uptake 12 weeks after initiation of WT1 immunotherapy. The percentage of the 3 categories was calculated 3-dimensionally and correlated with $OS_{WT1}$ (Fig. 5). While the percentage of the $PRM^{-MET}$ area showed moderate correlation with $OS_{WT1}$ ($p = 0.100$) (Fig. 5 left), the percentage of the $PRM^{+MET}$ area showed excellent correlation with $OS_{WT1}$ ($p = 0.008$) (Fig. 5 right). A threshold of 5% for $PRM^{+MET}$ yielded the best performance for discriminating WT1 immunotherapy responders from nonresponders (Fig. 5 right). When a Cox proportional hazard model was applied, adjusted by age (cutoff 50 years of age) and performance status (0 or 1 and 2), a threshold of 5% for $PRM^{+MET}$ still remained as the only statistically significant factor ($p = 0.01$).

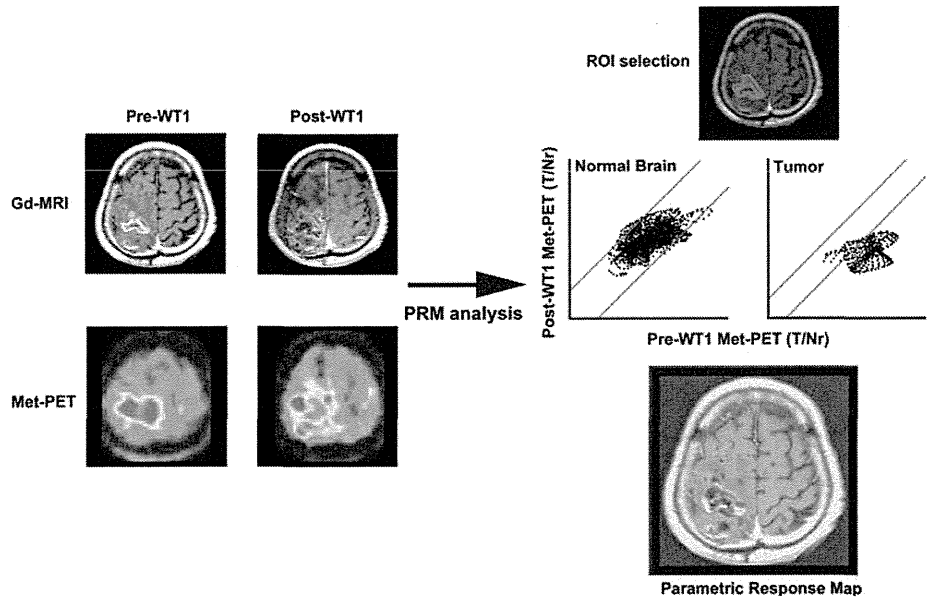


**Fig. 2.** Case 2. A representative treatment responder with recurrent GBM ($OS_{WT1}$ 144.7 weeks). Images were analyzed as in Fig. 1. Voxel-wise PRM analysis revealed that most of the contrast-enhanced lesion was within the $PRM^{-MET}$ area. Although the $OS_{WT1}$ was 144.7 weeks, conventional MR imaging evaluated the response as progressive disease. Gd-MRI = Gd-enhanced MR imaging; T/Nr = T/N max.

## Discussion

Conventionally, MR imaging is used to evaluate response to treatment in glioma patients. The maximum length of the contrast-enhanced area is measured and the effect of treatment is analyzed according to RECIST. This method is based on previous reports showing RECIST to be useful in determining objective responses of contrast-enhancing brain tumors to therapy. Moreover, those reports showed that use of RECIST was comparable to volumetric methods.[5,16] On the other hand, problems with using MR imaging–based tumor measurement as an indicator of treatment response have been reported. For example, temozolomide-based chemoradiotherapy for

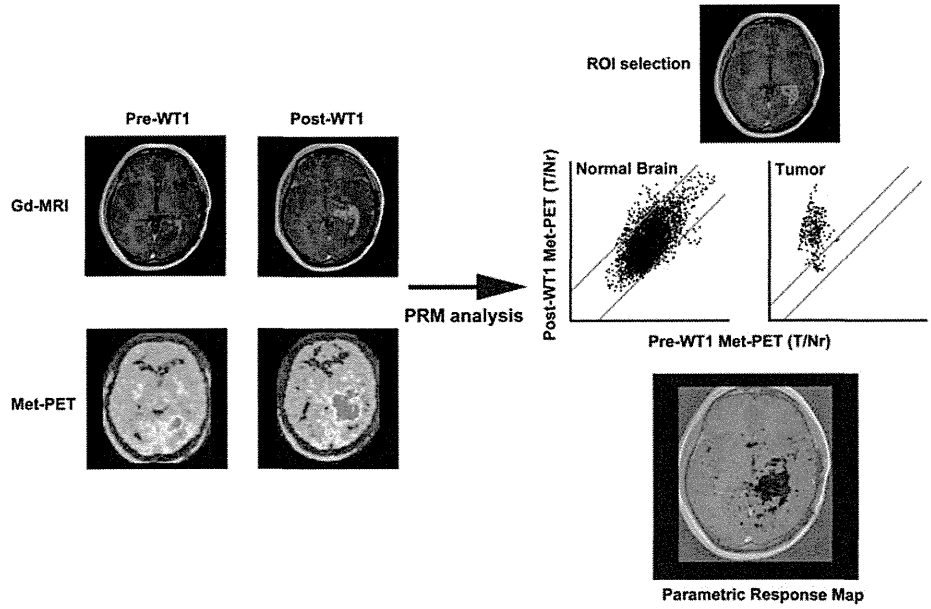


**Fig. 3.** Case 7. A representative treatment nonresponder with recurrent GBM ($OS_{WT1}$ 20.9 weeks). Images were analyzed as in Fig. 1. Voxel-wise PRM analysis revealed that most of the contrast-enhanced lesion was within the $PRM^{+MET}$ area, suggesting that the patient was not responsive to WT1 immunotherapy.

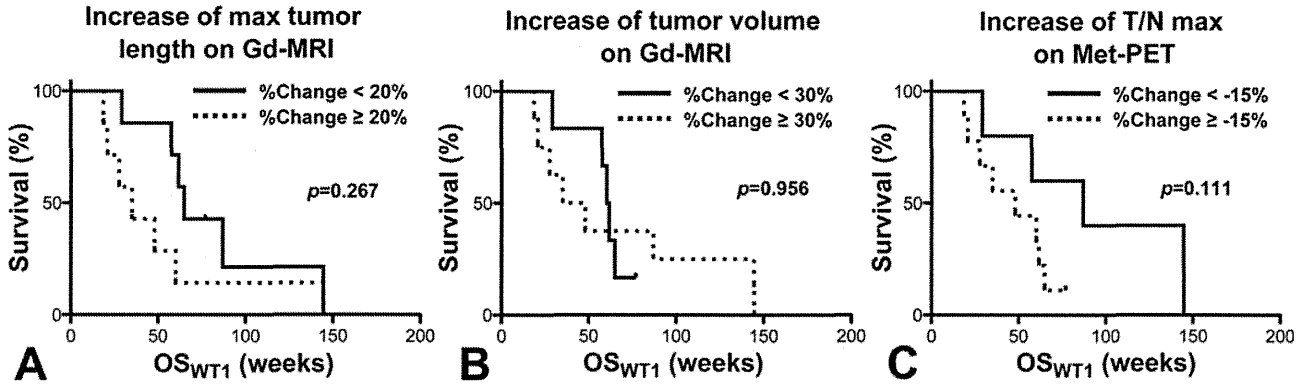


**Fig. 4.** Correlation of $OS_{WT1}$ with changes in tumor length and volume using contrast-enhanced MR imaging and the T/N max of MET-PET. Correlations between $OS_{WT1}$ and changes (from before WT1 immunotherapy to 12 weeks after immunotherapy initiation) on Gd-enhanced MR imaging–measured tumor length **(A)**, volume **(B)**, and T/N max of MET-PET **(C)** are presented. The correlations were not statistically significant (p = 0.270, 0.960, and 0.110, respectively; 14 cases).

newly diagnosed GBM results in a transient increase in tumor enhancement on MR imaging in 20%–30% of patients (pseudoprogression), which is difficult to differentiate from true tumor progression.[2] Similarly, in the present study, changes in tumor length and volume measured by contrast-enhanced MR imaging after WT1 immunotherapy did not correlate with $OS_{WT1}$ (Fig. 4), suggesting that contrast-enhanced MR imaging is inappropriate for evaluating the clinical outcome of WT1 immunotherapy. Unlike chemotherapy or radiotherapy, immunotherapy causes an inflammatory reaction in the tumor, which results in infiltration of inflammatory cells, dilation of capillary vessels, and increased capillary permeability. Thus, it is possible that contrast enhancement does not reflect the tumor activity but rather represents the immune reaction in situ.

On the other hand, MET-PET provides high-resolution metabolic information about the tumor in vivo,[10] information that is impossible to obtain using MR imaging. Previous studies have shown that the ratio of the maximum $^{11}$C-methionine uptake in tumor compared with the contralateral normal brain (T/N max) reflects prognosis.[4,11] However, gliomas are heterogeneous in nature and have heterogeneous uptake of $^{11}$C-methionine. In fact, we have previously demonstrated that $^{11}$C-methionine uptake correlates with tumor cell density by comparing MET-PET images with stereotactically sampled tissue.[15] Thus, instead of analyzing T/N max, which could result in comparisons between different locations within the tumor, a better method is to analyze the change in $^{11}$C-methionine uptake in each anatomical location to elucidate the global change in $^{11}$C-methionine uptake within the tumor. To satisfy this need, a voxel-wise PRM analysis[6–8] was used in the present study and produced excellent correlation between $OS_{WT1}$ and the percentage of $PRM^{+MET}$ (Fig. 5). This method showed far better correlation with $OS_{WT1}$ than changes in T/N max by MET-PET, suggesting that the voxel-wise PRM is the most suitable method for assessing the treatment response of gliomas. Moreover, although the number of cases analyzed was small, a threshold of 5% for $PRM^{+MET}$ was the best indicator for discriminating WT1 immunotherapy responders from nonresponders in terms of survival time (Fig. 5 right). A similar method has already been applied for diffusion or perfusion MR im-

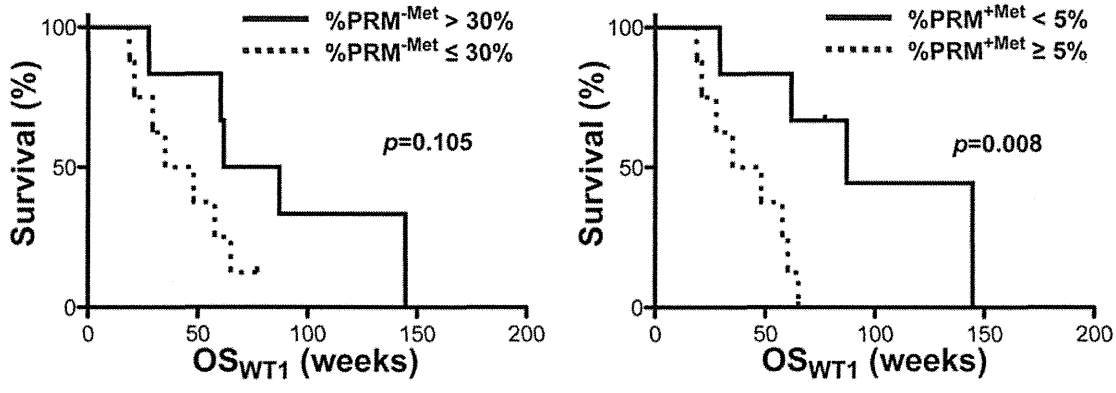


**Fig. 5.** Correlation of $OS_{WT1}$ with $PRM^{-MET}$ and $PRM^{+MET}$. Correlations between $OS_{WT1}$ and percentage areas of $PRM^{-MET}$ **(left)** and $PRM^{+MET}$ **(right)** are presented. The percentage of $PRM^{+MET}$ within the contrast-enhanced lesion before WT1 immunotherapy initiation correlated best with $OS_{WT1}$ (p = 0.008; 14 cases).

aging analysis in glioma treatment using temozolomide and radiation therapy and has been suggested as an early biomarker for treatment response.[6–8] The main difference between voxel-wise PRM analysis and conventional imaging analysis is that voxel-wise PRM analysis allows us to identify the location and extent of areas that responded to therapy, rather than comparing the maximum values of the pre- and posttreatment evaluation modality, which could be comparing different locations.

There are, however, limitations that should be noted. Because pre- and posttreatment $^{11}$C-methionine uptake is registered and compared, this method cannot be used when the shape or size dramatically change during therapy due to cyst formation or intratumoral hemorrhage. A more advanced method that could correct for tissue deformation is required to compensate for these changes. As the images compared were obtained 12 weeks apart, it is necessary to investigate the possibility of comparing images obtained in shorter intervals. Another limitation of this study is the retrospective nature of the data analysis and the limited sample size. Although a 5% cutoff of PRM$^{+MET}$ yields the best result for the survival analysis, a prospective study with a much larger sample size will be necessary to obtain the most suitable cutoff value. Moreover, other modalities, such as perfusion or diffusion MR images should also be investigated in a similar manner to elucidate whether these modalities could also be used for evaluating immunotherapy for malignant gliomas.

## Conclusions

We performed a voxel-wise PRM analysis of MET-PET before and 12 weeks after WT1 immunotherapy initiation to evaluate the clinical responses to WT1 immunotherapy in recurrent malignant glioma patients. This method holds promise for evaluating the dynamics of immunotherapy, which can be difficult to assess using conventional Gd-enhanced MR imaging.

### Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. This work was supported in part by grants to Dr. Kinoshita from the Osaka Cancer Research Foundation, the Konica Minolta Imaging Science Foundation, the Osaka Cancer Researcher Training Fund, the Takeda Science Foundation, the Sagawa Foundation for Promotion of Cancer Research, and the Ministry of Education, Science and Culture of Japan, and by grants to Drs. Chiba and Hashimoto from the Ministry of Education, Science and Culture of Japan.

Author contributions to the study and manuscript preparation include the following. Conception and design: Kinoshita, Chiba, Tsuboi, Hashimoto, Yoshimine. Acquisition of data: Kinoshita, Chiba, Okita, Tsuboi, Isohashi, Kagawa, Fujimoto, Oji, Oka, Shimosegawa, Hatazawa, Hashimoto, Yoshimine. Analysis and interpretation of data: all authors. Drafting the article: Kinoshita, Chiba, Okita, Morita, Hashimoto, Yoshimine. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kinoshita. Statistical analysis: Kinoshita. Administrative/technical/material support: Tsuboi, Hashimoto, Yoshimine. Study supervision: Tsuboi, Oji, Oka, Hatazawa, Hashimoto, Yoshimine.

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ORIGINAL ARTICLE

# A randomized phase-II trial comparing sequential and concurrent paclitaxel with oral or parenteral fluorinated pyrimidines for advanced or metastatic gastric cancer

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**Abstract**
*Background* The purpose of this study was twofold: (1) to compare S-1 with infusional 5-fluorouracil (FU) to determine which would be a better partner of paclitaxel (PTX), and (2) to compare a concurrent strategy with a sequential one, the latter strategy being the one that is widely used in Japanese general practice.
*Methods* The 161 eligible patients were randomized into four arms to receive the following regimens: A (sequential), intravenous 5-FU at 800 mg/m$^2$ for 5 days every 4 weeks followed by weekly PTX at 80 mg/m$^2$; B (sequential), S-1 at 80 mg/m$^2$ for 4 weeks and 2-week rest followed by PTX; C (concurrent), intravenous 5-FU at 600 mg/m$^2$ for 5 days and weekly PTX at 80 mg/m$^2$ every 4 weeks; and D (concurrent), S-1 for 14 days and PTX at 50 mg/m$^2$ on days 1 and 8 every 3 weeks. The primary endpoint was the overall survival (OS) rate at 10 months.
*Results* The ten-month OS rates in arms A, B, C, and D were 63, 65, 61, and 73%, respectively. The OS was best in the concurrent S-1/PTX arm, with a mean survival time of

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15.4 months, but no significant difference was observed between the four arms. Response rates were higher in the concurrent arms than in the sequential arms.

*Conclusion* Our study did not show sufficient prolongation of survival with the concurrent strategy to proceed to a phase-III trial; however, the sequential arms showed survival comparable to that in the concurrent arms, with less toxicity. In patients who are ineligible for cisplatin (CDDP), sequential treatment starting with S-1 and proceeding to PTX would be a good alternative strategy, considering quality of life (QOL) and the cost-benefits of an oral agent as first-line treatment.

**Keywords** Advanced gastric cancer · Paclitaxel · S-1 · Sequential chemotherapy · Concurrent combination chemotherapy · Randomized phase-II trial

## Introduction

Gastric cancer is the second most common cause of cancer-related death worldwide [1]. Most patients (except those from northeast Asian countries) present with advanced, inoperable, or metastatic disease, and the 5-year survival rate is approximately 10–15%. Palliative chemotherapy for advanced disease improves survival as compared with the best supportive care [2–4]. Despite the innumerable efforts of investigators in various countries to test various chemotherapeutic and immunotherapeutic agents and combination regimens, there has been little progress in the therapy for patients with advanced gastric cancer.

Probably because there is less evidence regarding the treatment of gastric cancer compared to that of other malignancies, the standard treatment for gastric cancer differs from country to country, although most of the "standard" regimens do not have sufficient evidence. Moreover, the insurance systems in most western countries approve only first-line treatment, and in these countries, doublet or triplet therapies could be the standard choice, while some countries, including Japan, approve second- and greater-line strategies, where we can choose not only concurrent but also sequential strategies. Reflecting these historical and social circumstances, "standard" treatment for gastric cancer shows wide variety, with some confusion. In Japan, the evidence-based standard regimen involved continuous infusion of 5-fluorouracil (5-FU) only (JCOG9205) before the results of the Japan Clinical Oncology Group (JCOG) 9912 and SPIRITS trials had been obtained [5–7]. After the results of SPIRITS trial were shown, S-1 plus cisplatin (CDDP) has been accepted as the standard first-line treatment for patients with good condition, but S-1 without CDDP was also widely used in general practice. This means we still need an alternative strategy, whose sequence starts from a fluoropyrimidine (infusional 5-FU or oral S-1) with or without other agents.

As for candidates as the fluoropyrimidine partner, some potent agents have been approved for gastric cancer in the past two decades. One of the promising agents was paclitaxel (PTX) [8], which had shown beneficial results in single use or concurrent use with a fluoropyrimidine [9–12]. However, these studies were conducted as single-arm phase I–II trials. Hence, the choice between sequential and concurrent strategies for fluoropyrimidine and PTX remains unclear.

We therefore planned a randomized phase-II trial to compare the following four treatment regimens: A, sequential 5-FU monotherapy followed by PTX monotherapy; B, sequential S-1 monotherapy followed by PTX monotherapy; C, concurrent 5-FU plus PTX [11]; and D, concurrent S-1 plus PTX [12]. The purpose of the study was twofold: (1) to compare S-1 with infusional 5-FU to determine which was the better partner of PTX, and (2) to compare a concurrent strategy with a sequential one, the latter strategy being the one that is widely used in Japanese general practice.

## Patients and methods

The detailed study design and protocol treatment of this study has already been described by Morita et al. [13]. Below we outline a summary of the methodological issues in this study with the protocol (informed consent form) that was amended after the SPIRITS trial.

### Eligibility criteria

Patients more than 20 years of age with histologically confirmed non-resectable advanced or recurrent gastric cancer were eligible. Patients who had undergone prior anti-tumor therapy (except for surgery and postoperative adjuvant chemotherapy) were excluded. Patients had to have adequate renal, hepatic, hematologic, and cardiac function, with an Eastern Cooperative Oncology Group performance status (PS) of 0–1. Patients had to be able to take food via the oral route to be considered for enrolment in the study.

The protocol was approved by the Institutional Review Board (IRB) of each institution, and written informed consent was obtained before treatment. Participating investigators were instructed to send an eligibility criteria report to the data center operated by the non-profit organization Epidemiological and Clinical Research Information Network (ECRIN). Eligible patients were registered and then randomized to receive either of the four treatment regimens (A, B, C, and D), using a centralized dynamic

randomization method with the following balancing factors: measurable disease according to criteria set by Response Evaluation Criteria in Solid Tumours (yes/no); disease type [inoperable advanced/postoperative recurrent (with postoperative chemotherapy)/postoperative recurrent (with no postoperative chemotherapy)]; PS (0/1); peritoneal metastasis based on diagnosis with images (yes/no); age (<75 years/≥75 years), and institution. Information regarding the necessary follow-up examinations and chemotherapy schedule was then sent from the ECRIN data center. The accrual started in December 2005 and was continued for 3 years.

### Projected treatments

Based on previous trials, we adapted four promising regimens for this selection design trial [13]. Patients in arm A received sequential therapy with intravenous (i.v.) 800 mg/m$^2$ 5-FU daily for 5 days every 4 weeks until progression, followed by PTX 80 mg/m$^2$ on days 1, 8, and 15 every 4 weeks. Patients in arm B received sequential therapy with 80 mg/m$^2$ of oral S-1 daily for 4 weeks and 2-week rest after the administration (total of 6 weeks per single course) until progression. This was followed by PTX, utilizing the same administration dose and schedule as that in arm A's second-line PTX. Patients in arm C received a combination therapy with 600 mg/m$^2$ 5-FU (i.v.) daily for 5 days from day 1 and infusion of 80 mg/m$^2$ PTX on days 8, 15, and 22 every 4 weeks. Patients in arm D received a combination therapy with 80 mg/m$^2$ oral S-1 for 14 days from day 1 and infusion of 50 mg/m$^2$ PTX on days 1 and 8 every 3 weeks. In the sequential treatment arms A and B, the administration of 5-FU or S-1 monotherapy was discontinued if the following were observed: (1) disease progression or occurrence of new disease; (2) grade-4 nonhematological toxicities evaluated according to the Common Terminology Criteria for Adverse Events version 3.0; (3) adverse events causing patients to refuse treatment or causing a clinician to discontinue treatment; (4) increase in the tumor markers carcinoembryonic antigen (CEA) and/or cancer antigen (CA) 19-9 in two or more consecutive measurements or symptomatic progression (e.g., cancer pain and dysphagia). An irinotecan-containing regimen was recommended for use in case further lines of treatment were to be given.

### Follow-up

Disease progression and occurrence of new disease were examined using radiographs, computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen, and thoracic CT and measurements of the tumor markers CEA and CA19-9. These examinations were performed at baseline and at least every 4–5 weeks during treatment. Blood tests and symptom checks were performed before treatment and at least every 2 weeks during treatment. In cases where therapy was discontinued owing to toxicity, clinicians followed up patients until they recovered from the effects of toxicity.

### Study design and statistical methods

The primary aim of this study was to compare treatment regimens A–D in terms of the primary endpoint of the 10-month overall survival (OS) rate. In addition, OS and treatment failure curves were constructed as time-to-event plots using the Kaplan–Meier method [14]. Time-to-event curves were compared using log-rank tests and the hazard ratio (HR) estimated by Cox regression models [15]. The prevalence of grade-3 or grade-4 adverse events was compared between the treatment arms. Calculation of the sample size required 40 patients in each arm to assure 80% probability in order to select the best treatment arm [16] as long as the true expected 10-month OS rate exceeded that of any other arm by at least 15%. The total number of patients to be accrued was set at 160.

### Protocol amendment after SPIRITS trial

After the results of the SPIRITS trial were publicized, standard first-line therapy in Japan shifted from monotherapies with 5-FU or S-1 to an S-1/CDDP combination. The protocol committee of the present trial discussed this issue and decided not to change the protocol treatments, because none of the treatment arms has actually been shown to be inferior to the S-1/CDDP combination. Instead, all patients who became candidates for accrual in the trial after the results of the SPIRITS trial were publicized were to be informed of the novel standard treatment in Japan, using a newly compiled explanatory note, and they were to be offered the alternative of receiving the combination therapy instead of participating in the trial. Each participating institution agreed on the use of the newly compiled explanatory note without correction in the study protocol itself, and case recruitment was re-started after the IRB approval of the amendment was obtained.

## Results

A total of 161 patients were enrolled in the trial from December 2005 to November 2008. The numbers of patients in arms A, B, C, and D were 40, 40, 41, and 40, respectively. Two patients in arm A and two in arm C declined therapies before the start of the assigned treatment. Therefore, 38, 40, 39, and 40 patients in arms A, B,

C, and D, respectively, were considered to be eligible for evaluation (Fig. 1). Initial patient characteristics in the four arms were well matched (Table 1). The median age was 67 years (range 40–90 years).

## Survival

The ten-month OS rates predetermined as the primary endpoint were 63, 65, 61, and 73% in arms A, B, C, and D, respectively. Although concurrent therapy with S-1 plus PTX demonstrated the best survival benefit among the four arms, the difference in OS rates between the arms with highest (D) and lowest (C) rates was less than the predetermined criterion (i.e., 15%). Kaplan–Meier survival curves did not show a significant difference between the four arms (Fig. 2). The survival rates in the sequential (A, B) and concurrent (C, D) arms were almost identical ($p = 0.93$) (Fig. 3a). In addition, no difference in survival was observed between the 5-FU-containing regimens (arms A and C) and the S-1-containing regimens (arms B and D) ($p = 0.83$) (Fig. 3b).

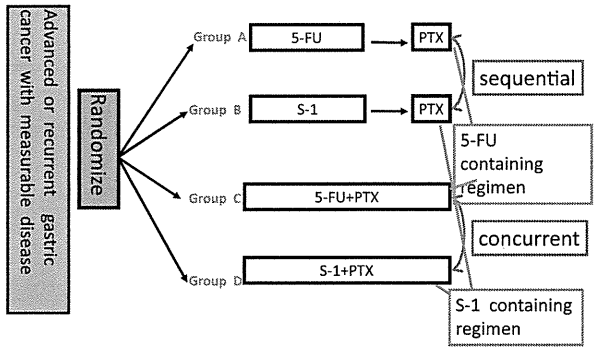


**Fig. 1** CONSORT diagram that accounts for all patients. *5-FU* 5-fluorouracil, *PTX* paclitaxel

## Time to treatment failure (TTF)

In arms A and B, TTF was calculated by the addition of the prior 5-FU or S-1 treatment period and the sequential PTX period. Median TTF values were 213, 222, 177, and 189 days in arms A, B, C, and D, respectively. No difference was observed between the four arms. However, Kaplan–Meier TTF curves for sequential and concurrent regimens showed better TTF in favor of sequential treatment compared with concurrent treatment (HR 0.71, 95%

**Table 1** Patient characteristics

| Treatment arm | Arm A 5-FU→PTX $n = 38$ | Arm B S-1→PTX $n = 40$ | Arm C 5-FU+PTX $n = 39$ | Arm D S-1+PTX $n = 40$ |
|---|---|---|---|---|
| Gender | | | | |
| Male | 25 (65.8%) | 28 (70.0%) | 28 (71.8%) | 32 (80.0%) |
| Female | 13 (34.2%) | 12 (30.0%) | 11 (28.2%) | 8 (20.0%) |
| Age (years) | | | | |
| Median | 67.0 | 68.0 | 67.3 | 66.6 |
| Range | 48–79 | 51–81 | 40–82 | 47–90 |
| 74≤ | 31 (81.6%) | 33 (82.5%) | 31 (79.5%) | 31 (77.5%) |
| ≤75 | 7 (18.4%) | 7 (17.5%) | 8 (20.5%) | 9 (22.5%) |
| Performance status | | | | |
| 0 | 29 (76.3%) | 27 (67.5%) | 25 (64.1%) | 28 (70.0%) |
| 1 | 9 (23.7%) | 13 (32.5%) | 14 (35.9%) | 12 (30.0%) |
| Stage | | | | |
| Non-resectable, no previous chemotherapy | 31 (81.6%) | 33 (82.5%) | 32 (82.1%) | 32 (80.0%) |
| Recurrent after curative surgery, adjuvant chemotherapy (+) | 2 (5.3%) | 1 (2.5%) | 3 (7.7%) | 3 (7.5%) |
| Recurrent after curative surgery, adjuvant chemotherapy (–) | 5 (13.2%) | 6 (15.0%) | 4 (10.3%) | 5 (12.5%) |
| Peritoneal metastasis | | | | |
| Yes | 9 (23.7%) | 13 (32.5%) | 5 (12.8%) | 10 (25.0%) |
| No | 29 (76.3%) | 27 (67.5%) | 34 (87.2%) | 30 (75.0%) |
| Measurable disease | | | | |
| Yes | 19 (50.0%) | 23 (57.5%) | 17 (43.6%) | 20 (50.0%) |
| No | 19 (50.0%) | 17 (42.5%) | 22 (56.4%) | 20 (50.0%) |

*5-FU* 5-fluorouracil, *PTX* paclitaxel

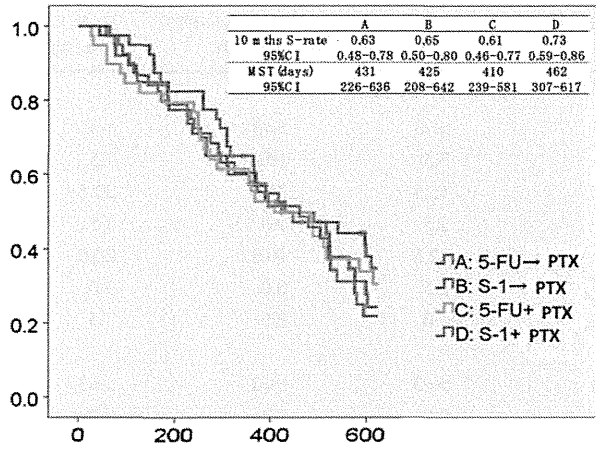


**Fig. 2** Kaplan–Meier plot of overall survival in the four treatment arms. *S-rate* survival rate, *CI* confidence interval, *MST* median survival time

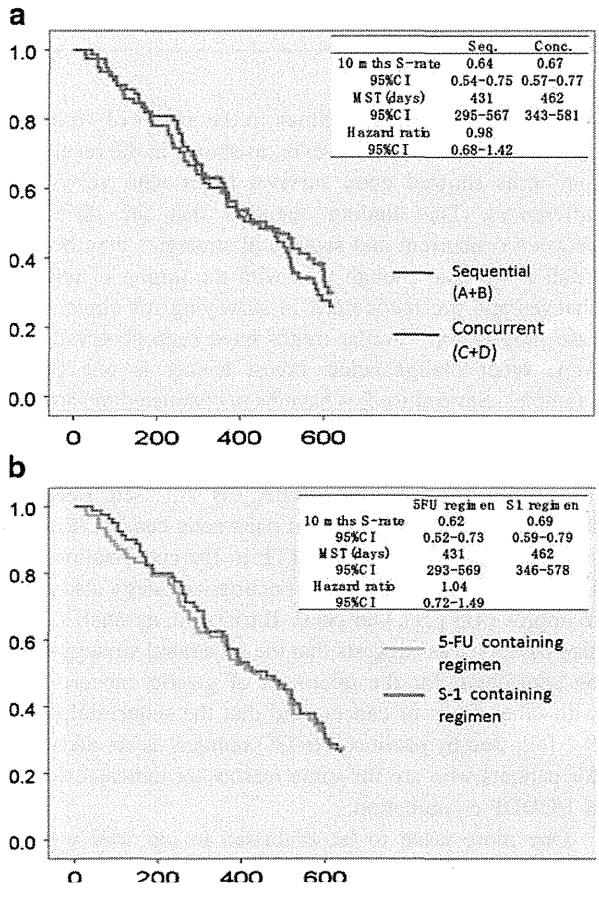


**Fig. 3** Kaplan–Meier plot of overall survival by **a** sequential regimens (arms *A* and *B*) and concurrent regimens (arms *C* and *D*), **b** 5-FU-containing regimens (arms *A* and *C*) and S-1-containing regimens (arms *B* and *D*). *seq.* sequential, *conc.* concurrent

**Table 2** Tumor response rates

| Treatment arm/agent | *n* (With measurable lesion) | CR | PR | SD | PD | Response rate (%) |
|---|---|---|---|---|---|---|
| A | | | | | | |
| 5-FU | 17 | 0 | 5 | 8 | 4 | 29.4 |
| PTX | 17 | 0 | 2 | 10 | 5 | 11.8 |
| B | | | | | | |
| S-1 | 20 | 1 | 4 | 10 | 5 | 25.0 |
| PTX | 14 | 1 | 1 | 10 | 2 | 14.3 |
| C | | | | | | |
| 5-FU + PTX | 13 | 0 | 9 | 2 | 2 | 69.2 |
| D | | | | | | |
| S-1 + PTX | 19 | 1 | 7 | 11 | 0 | 42.1 |

*CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

confidence interval [CI] 0.50–1.02, $p = 0.06$). A difference in TTF was not observed between the 5-FU-containing and S-1-containing regimens.

## Response rates

The overall response rates in patients who had measurable disease are summarized in Table 2. Response rates were higher in the concurrent arms than in the sequential arms. The 5-FU and PTX combination regimen showed the best response rate among the four arms.

## Toxicities

All patients could be assessed for hematological and non-hematological toxicities (Table 3). Ten of 78 patients (12.8%) who received sequential therapy and 26 of 79 patients (33.0%) who received concurrent therapy showed grade-3 or grade-4 neutropenia. With respect to hemoglobin decrease, 21 patients (26.2%) with the S-1-containing regimens showed grade-3 or grade-4 adverse events, whereas only 8 patients (10.4%) with the other regimens showed adverse events. No difference was observed in non-hematological toxicity.

## Compliance

Compliance with S-1 treatment was inferior to that with 5-FU treatment. The median numbers of courses accomplished in the first- and second-line treatment of the

**Table 3** Toxicities

| | A: 5-FU→PTX ($n$ = 38) | B: S-1→PTX ($n$ = 40) | C: 5-FU+PTX ($n$ = 39) | D: S-1+PTX ($n$ = 40) |
|---|---|---|---|---|
| Hematological toxicities | | | | |
| CTC Grade | >=3 | >=3 | >=3 | >=3 |
| Leucopenia (%) | 7.9 | 7.5 | 10.3 | 7.5 |
| Neutropenia (%) | 13.2 | 12.5 | 25.6 | 22.5 |
| Thrombocyte (%) | 0.0 | 2.5 | 0.0 | 2.5 |
| Hemoglobin (%) | 10.5 | 32.5 | 10.3 | 20.0 |
| Total Bil (%) | 2.6 | 2.5 | 0.0 | 5.0 |
| Hepatic Tox (%) | 7.9 | 5.0 | 2.6 | 7.5 |
| Non-hematological toxicities | | | | |
| CTC Grade | >=3 | >=3 | >=3 | >=3 |
| Weight loss (%) | 2.6 | 0.0 | 2.6 | 0.0 |
| Fatigue (%) | 0.0 | 0.0 | 0.0 | 0.0 |
| Lassitude (%) | 7.9 | 12.5 | 5.1 | 10.0 |
| Anorexia (%) | 10.5 | 12.5 | 7.7 | 10.0 |
| Nausea (%) | 2.6 | 5.0 | 5.1 | 2.5 |
| Vomiting (%) | 0.0 | 0.0 | 2.6 | 0.0 |
| Stomatitis (%) | 5.3 | 0.0 | 2.6 | 2.5 |
| Diarrhea (%) | 2.6 | 2.5 | 5.1 | 2.5 |
| Neuropathy (%) | 0.0 | 2.5 | 5.1 | 5.0 |

*CTC* Common Toxicity Criteria

sequential regimens were 4 (range 1–26) and 3 (range 1–8) in arm A and 6 (range 1–24) and 4 (range 1–30) in arm B, respectively. For the concurrent regimens, these numbers were 6 (range 1–24) and 7.5 (range 1–30) in arms C and D, respectively.

## Discussion

The strategy for the chemotherapy of gastric cancer differs from country to country. In Japan, according to community standards, fluoropyrimidine monotherapy has been widely used as the first-line of a sequential strategy, whereas most western countries use doublet or triplet concurrent regimens without second-line treatment. In fact, little is known about whether concurrent regimens or a sequential strategy with satisfactory second- and greater-line treatments would be better. Although one trial has shown the superiority of doublet (S-1 with CDDP) treatment compared with S-1 alone even in Japan [7], other pivotal trials have failed to show the superiority of concurrent regimens [17, 18]. This suggests that sequential strategies may not be so bad if we can use adequate second- (and more)-line therapies in sequence. Thus, when we decided to evaluate PTX in a clinical trial, we created the study plan so as to evaluate whether PTX should be used in second-line (sequential) or in first-line (concurrent) treatment.

In accordance with the general rule in a randomized phase-II trial, in the present study we assumed that we should choose the best regimen in the aspect of 10-month overall survival (OS). However, as shown in the results, all four arms showed good survival times with very small differences. This finding suggests that the difference between concurrent and sequential strategies may be very small if we take enough care with the timing of regimen changes and are meticulous in surveying for clinical disease progression. Similar trends have been observed with some other malignancies; breast cancer is one of the examples. Several studies have been conducted to show the survival superiority of concurrent regimens, but superiority was seen only in TTF and the response rate (RR) [19, 20]. As a result, the sequential strategy is still used. Recently, the result of the GEST trial in pancreatic cancer showed a superior RR and a superior TTF in the combination arm. Despite this superiority, this concurrent strategy also failed to improve OS [21]. Our phase-II trial with its small sample size nevertheless suggests that the sequential strategy could be considered for the treatment of gastric cancer, along with other types of cancer, and that the sequential use of S-1 followed by paclitaxel (PTX) remains as an alternative for patients who are for some reason not indicated for the S-1/CDDP combination.

One more issue to be evaluated in our trial was the difference between infusional 5-FU and oral S-1. The results of a worldwide advanced gastric cancer trial (FLAGS trial) comparing S-1 plus CDDP (SF) versus 5-FU plus CDDP (CF) failed to show a superior effect of SF over CF [22]. The JCOG9912 trial has already shown no