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Factors affecting enrollment in randomized controlled trials conducted for patients with metastatic breast cancer

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Abstract

Background: It is critical to obtain informed consent from eligible patients to complete clinical trials. We investigated the factors that affect the participation rates of eligible patients.

Patients and methods: Patients with metastatic breast cancer who were eligible for SELECT BC or SELECT BC-CONFIRM trials, randomized controlled trials conducted for patients with chemotherapy-naive metastatic breast cancer were recruited to prospective studies, SELECT BC-FEEL and SELECT BC-FEEL II, respectively. SELECT BC FEEL and SELECT BC-FEEL II were conducted to identify the factors affecting the rates at which informed consent was obtained, using a self-administered questionnaire we developed.

Results: In total, 232 patients participated in the studies. The patients who agreed to take part in the randomized trials were more likely than the refusers to answer that they decided to participate because: 'My doctor wanted me to participate in this trial' ($P = 0.00000$), ' My family or friends wanted me to participate in this trial' ($P = 0.00000$), 'Both treatment regimens used in the trial are suitable to me' ($P = 0.00383$), 'I know that the trial is conducted to determine which is a better

treatment' ($P = 0.01196$), and ' I think that my participation in the trial will contribute to the benefit to future patients with the same disease' ($P = 0.00756$).
Conclusions: To enhance the consent rate in randomized trials of metastatic breast cancer patients, concepts of the trials must be considered important and acceptable not only by patients but also by doctors and their families.

Key words: metastatic breast cancer, prospective cohort study, enrollment, informed consent

Introduction

Clinical trials are important for the advancement of clinical medicine. To accelerate completion of the trials, it is critical to obtain informed consent from eligible patients.

Thus, identifying factors affecting the participation of eligible patients are important. Although a lot of studies have addressed this issue in oncology (1–11), a few of them focused on specific cancers, such as breast cancer (1,9,10). The factors reported to affect participation rates in these studies may not be applicable to trials conducted for Japanese patients with breast cancer as participation rates may vary depending on factors such as sex, race, nationality and cultural background. Moreover, randomization is thought to be a barrier to obtaining consent (1,5,7,9). Randomized trials are crucial to improve standard treatments in clinical practice. Therefore, we investigated the factors affecting participation rates in randomized trials for breast cancer patients. We conducted prospective studies using a self-administered questionnaire that we developed.

Patients and methods

All patients who were eligible for SELECT BC or SELECT BC-CONFIRM trials were asked to take part in the prospective studies SELECT BC-FEEL (FEEL) and SELECT BC-FEEL II (FEEL II), respectively. Both SELECT BC and SELECT BC-CONFIRM were randomized controlled trials that compared taxanes or anthracyclines, respectively, with the oral regimen of S-1 in the first-line setting for patients with metastatic breast cancer (12,13). No inferiority was shown in S-1 compared with either taxanes or anthracyclines in terms of overall survival, which was the primary outcome. Both FEEL and FEEL II were additional studies that aimed to clarify factors that affect participation in randomized controlled trials of patients with metastatic breast cancer. We used a self-administered questionnaire to identify the factors. The questionnaire used was developed by our group and shown in the Appendix, and the process of the development was described previously (14). It included the following items: physician recommendation (B); family or friend recommendation (C); amount of explanation about the trial, from the doctor or clinical research coordinator (CRC) (D) and printed matter (E); agents used (F); understanding of the concept of the trial (G); benefit to others (H); relationship to the doctor (I); attitude towards random assignment (J); concerns about privacy (K), burden on the patient (L), and potential side effects (M); their age (O); prior chemotherapy (P); time needed to decide whether or not to participate (Q); communication with their doctor (R); communication with other patients (S); potential side effects they were concerned about (T); and other people's opinions that affected their decision (U).

The patients who were eligible to participate in SELECT BC or SELECT BC-CONFIRM were handed the questionnaire by the doctor in charge or a CRC. The completed questionnaires were collected within 1 month after patients informed the doctor of their decision. The CRCs who collected the questionnaires put the names and addresses of the hospitals and the names of the CRCs in charge on the backside of the envelopes, and sent them to our data center located in Tokyo by mail (14). The CRCs were blinded to the answers of the questionnaire in the envelope.

The primary outcome of these studies was to identify factors relating to clinical trial participation.

Patients were divided into two groups by their decision of whether or not to participate in one of the randomized trials. To investigate the associations between each patient's decision to participate in the trials and their responses to each question, two-sided *P*-values were calculated in the Chi-square test for binary comparisons, the Mann-Whitney's U test for questions that used three-point or five-point Likert scales, and the t-test for questions with continuous variables. *P*-values of <0.05 were considered statistically significant.

This study was registered at UMIN-CTR with number UMIN000 021243. The present study was approved by local ethical committees and oral informed consent was obtained from each patient. Analysis was performed at the CSPOR Data Center in Tokyo.

Results

FEEL and FEEL II were conducted between January 2010 and July 2010, and between June 2011 and January 2014, respectively, and 53 and 179 patients participated, respectively, from 47 institutions throughout Japan. Among the 232 FEEL or FEEL II participants, three did not state their decision, so they were excluded from the analyses (Fig. 1). The data from the two studies were analyzed separately; however, the results were quite similar between them (data not shown); therefore, the data shown below are the results of FEEL and FEEL II analyzed together.

In total, 185 patients (80.8%) participated and 44 refused.

Questions B-M, and S consisted of five-point Likert scales. Respondents who answered 'strongly agree' or 'agree to some extent' to the following statements were more likely to participate in the trials: (B) 'My doctor wanted me to participate in this trial' (participants 69.2% vs. refusers 25.6%; $P = 0.00000$), (C) 'My family or friends wanted me to participate in this trial' (46.7% vs. 9.3%; $P = 0.00000$), (F) 'Both treatment regimens used in the trial are suitable to me' (48.4% vs. 23.8%; $P = 0.00383$), (G) 'I know that the trial is conducted to determine which is a better treatment' (91.9% vs. 76.8%; $P = 0.01196$), and (H) 'I think that my participation in the trial will contribute to the benefit to future patients with the same

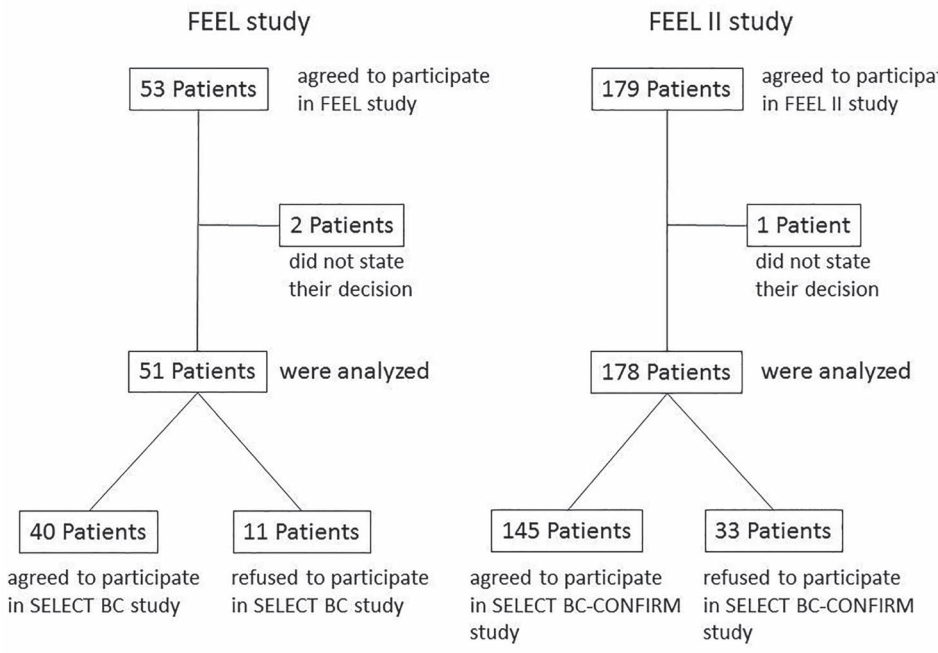

Figure 1 Flow diagram of the patients.

disease' (96.2% vs. 84.1%; $P = 0.00756$). However, the opposite was seen in (J) 'I am worried about the fact that I cannot choose which treatment to receive if I participate in the trial' (46.4% vs. 67.4%; $P = 0.00967$) (Tables 1 and 2).

The number of days taken to make a decision (Q) were significantly longer in the refusers than in the participants ($P = 0.0168$) (Table 3). There were no differences in the age (O), prior use of chemotherapy (P) and potential side effects that the patients were concerned about (T) between the two groups ($P = 0.9925$, 0.6814 and 0.7154, respectively).

The items that affected their decision the most were significantly different between the participants and refusers ($P < 0.0001$) (Table 3). The participants tended to answer (B), (D) and (H) more than the refusers. The persons who affected their decision the most were also significantly different between the two groups ($P = 0.0045$) (Table 3). The participants were more likely to answer 'their doctors' (participants 66.1% vs. refusers 39.5%), but the refusers answered 'their family' more frequently than the participants (22.8% vs. 46.5%).

Discussion

There are many studies that examined factors affecting cancer patients' decisions to participate in clinical trials (1–11). They include protocol-related, patient-related and physician-related factors. There are several types of cancer and patients' situations such as those with early-stage cancer and metastatic disease. Moreover, there are several styles of clinical trials, such as Phases I, II and III, and several types of interventions, such as chemotherapy, radiotherapy and surgery. Systematic reviews and meta-analyses investigated these factors (15). Mills et al. summarized the barriers to clinical trials including Phases I, II and III trials and reported that the most common reasons cited as barriers were concerns with the trial setting, a dislike of randomization, general discomfort with the research process, complexity and stringency of the protocol, presence of a placebo or no-treatment group, potential side effects, being unaware of trial opportunities, the idea that clinical trials are not appropriate for serious diseases, fear that trial involvement would have a negative effect on their relationship with their physician and their physician's attitude towards the trial (15). In general, patients' situations were quite different between Phases I or II and III. Since patients who are eligible for Phases I or II trials were generally those with incurable disease, they tended to consider the effect from the new treatments rather than potential benefits to other people, and it was relatively easy to obtain informed consent. However, it was more difficult to obtain consent to participate in Phase III trials from patients, because there are standard treatments, they can decline to participate without concern, and there is the barrier of randomization. Some studies showed that those who participate in randomized trials tended to score highly on altruism (7), but another study did not find that (9). Jenkins et al. (7) reported that acceptance of randomized trials was not dependent on disease stage, tumour type, sex or age, but they showed randomization and comparison of treatment duration were barriers. Most of the reports regarding factors associated with the acceptance of clinical trials in oncology were from western countries (1–3,5–11). However, decision-making may depend on factors such as sex, race, nationality and cultural background. Therefore, we focused on randomized trials that compared the efficacy between taxanes or anthracyclines and an oral regimen of S-1 in Japanese patients with metastatic breast cancer in the first-line setting.

This study was conducted to detect factors that could affect the patients' decisions to participate in randomized trials. Among these factors, their doctors affected the patients' decision the most (B). Therefore, if doctors want their patients to participate in a randomized trial, they should recommend for them to do so. Patients' family member(s) affected their decision as well. Therefore, if the

Table 1. Patients' answers to Questions B to M and S

	1	2	3	4	5	Sum
B_My doctor wanted me to participate in this trial						
Participants	49	79	54	2	1	185
%	26.5	42.7	29.2	1.1	0.5	
Refusers	2	9	30	1	1	43
%	4.7	20.9	69.8	2.3	2.3	
Sum	51	88	84	3	2	228
Missing Data = 1						
C_My family or friends wanted me to participate in this trial						
Participants	22	63	84	6	7	182
%	12.1	34.6	46.2	3.3	3.8	
Refusers	0	4	23	9	7	43
%	0	9.3	53.5	20.9	16.3	
Sum	22	67	107	15	14	225
Missing Data = 4						
D_I am satisfied with the explanation I received about this trial from my doctor or clinical research coordinator						
Participants	54	101	21	4	2	182
%	29.7	55.5	11.5	2.2	1.1	
Refusers	9	25	5	4	0	43
%	20.9	58.1	11.6	9.3	0	
Sum	63	126	26	8	2	225
Missing Data = 4						
E_I am satisfied with the explanation I received about this trial from printed matter						
Participants	45	91	43	3	3	185
%	24.3	49.2	23.2	1.6	1.6	
Refusers	5	25	10	2	1	43
%	11.6	58.1	23.3	4.7	2.3	
Sum	50	116	53	5	4	228
Missing Data = 1						
F_Both treatment regimens used in the trial are suitable to me						
Participants	19	69	83	9	2	182
%	10.4	37.9	45.6	4.9	1.1	
Refusers	3	7	26	5	1	42
%	7.1	16.7	61.9	11.9	2.4	
Sum	22	76	109	14	3	224
Missing Data = 5						
G_I know that the trial is conducted to determine which is a better treatment						
Participants	69	100	11	3	1	184
%	37.5	54.3	6.0	1.6	0.5	
Refusers	10	23	10	0	0	43
%	23.3	53.5	23.3	0	0	
Sum	79	123	21	3	1	227
Missing data = 2						
H_I think that my participation in the trial will contribute to the benefit to future patients with the same disease						
Participants	110	68	7	0	0	185
%	59.5	36.8	3.8	0	0	
Refusers	18	19	7	0	0	44
%	40.9	43.2	15.9	0	0	
Sum	128	87	14	0	0	229
Missing data = 0						
I_I think that my relationship with my doctor will become worse if I refuse to participate in the trial						
Participants	6	12	48	33	85	184
%	3.3	6.5	26.1	17.9	46.2	
Refusers	0	1	13	11	19	44
%	0	2.3	29.5	25.0	43.2	
Sum	6	13	61	44	104	228
Missing data = 1						

(Continued)

Table 1. Continued.

	1	2	3	4	5	Sum
J_I am worried about the fact that I cannot choose which treatment to receive if I participate in the trial						
Participants	41	44	52	20	26	183
%	22.4	24.0	28.4	10.9	14.2	
Refusers	16	13	8	4	2	43
%	37.2	30.2	18.6	9.3	4.7	
Sum	57	57	60	24	28	226
Missing data = 3						
K_I am concerned about leakage of my personal information if I participate in the trial						
Participants	3	5	34	41	101	184
%	1.6	2.7	18.5	22.3	54.9	
Refusers	0	5	8	13	18	44
%	0	11.4	18.2	29.5	40.9	
Sum	3	10	42	54	119	228
Missing data = 1						
L_I am concerned about an increased burden on me if I participate in the trial						
Participants	7	36	61	32	49	185
%	3.8	19.5	33.0	17.3	26.5	
Refusers	4	7	17	8	8	44
%	9.1	15.9	38.6	18.2	18.2	
Sum	11	43	78	40	57	229
Missing data = 0						
M_I am concerned about the side effects of the treatments used in the trial, if I participate in it						
Participants	51	76	39	10	8	184
%	27.7	41.3	21.2	5.4	4.4	
Refusers	11	16	7	4	6	44
%	25.0	36.4	15.9	9.1	13.6	
Sum	62	92	46	14	14	228
Missing data = 1						
S_Do you want to know what questions other patients who received the explanation about this trial asked their doctors?						
Participants	37	57	63	10	17	184
%	20.1	31.0	34.2	5.4	9.2	
Refusers	6	13	22	1	2	44
%	13.6	29.5	50.0	2.3	4.5	
Sum	43	70	85	11	19	228
Missing data = 1						

1, strongly agree; 2, agree to some extent; 3, unsure; 4,disagree to some extent; 5, strongly disagree. Data of FEEL and FEEL II were combined.

patients' family member(s) listen to the explanation about the trial with the patient, the doctors or CRCs should convince them of the significance of the trial too. In addition, both (F) 'Both treatment regimens used in the trial are suitable to me', and (G) 'I know that the trial is conducted to determine which is a better treatment' affected the patients' decision positively. This means that the study design must be good in quality and fair to everybody, and doctors or CRCs must recommend the trial participation to the patients confidently.

The strong points of this study are a relatively large size and prospective design. There were several limitations to this study. First, not all of the patients who were offered to participate in the randomized trials were patients of FEEL and FEEL II; therefore, there may have been a selection bias. Only 53 patients participated in the FEEL study compared with 618 who enrolled in the SELECT BC trial, as FEEL started late in the recruitment of patients for SELECT BC. On the other hand, FEEL II, which recruited 179 patients, started at the same time as SELECT BC-CONFIRM, in which 230 patients were enrolled. Second, the patients were those with metastatic breast cancer, candidates of first-line chemotherapy, and were offered to participate in the randomized trial. Therefore, our results may not be applicable to other types of patients and other situations such as early-stage lung cancer patients. However, the results of 'Recommendations of the doctors and families of the patients are important' are likely applicable to various cancer patients and situations. Third, the acceptance rate of 80.8% (185/229) in our study is extremely high, compared with the results of other studies. For example, Avis et al. (1) reported that the corresponding rate in Phase III trials was 51.8%. The high acceptance may have been caused by the study concept of SELECT BC and SELECT BC-CONFIRM that seemed to be easily accepted by both the patients and their doctors. Namely, S-1 was an approved and frequently used drug for metastatic breast cancer in the second or later line setting in Japan when the trials were open, but this high acceptance rate may have affected the results.

Table 2. The statistical results of the numerical comparisons of the answers between the participants and refusers

Questions	1: participatants; 2: refusers	Data obtained	Missing data	Mean	Standard deviation	50th Percentile (median)	*P*-values (t-test)	*P*-values (Mann-Whitney's U test)
B_My doctor wanted me to participate in this trial	1	185	0	2.0649	0.8049	2	0.00000	0.00000
B_My doctor wanted me to participate in this trial	2	43	1	2.7674	0.6844	3		
C_My family or friends wanted me to participate in this trial	1	182	3	2.5220	0.8901	3	0.00000	0.00000
C_My family or friends wanted me to participate in this trial	2	43	1	3.4419	0.8811	3		
D_I am satisfied with the explanation I received about this trial from my doctor or clinical research coordinator	1	182	3	1.8956	0.7689	2	0.13833	0.16107
D_I am satisfied with the explanation I received about this trial from my doctor or clinical research coordinator	2	43	1	2.0930	0.8399	2		
E_I am satisfied with the explanation I received about this trial from printed matter	1	185	0	2.0703	0.8278	2	0.13748	0.14932
E_I am satisfied with the explanation I received about this trial from printed matter	2	43	1	2.2791	0.8259	2		
F_Both treatment regimens used in the trial are suitable to me	1	182	3	2.4835	0.7917	3	0.00659	0.00383
F_Both treatment regimens used in the trial are suitable to me	2	42	2	2.8571	0.8136	3		
G_I know that the trial is conducted to determine which is a better treatment	1	184	1	1.7337	0.6933	2	0.02417	0.01196
G_I know that the trial is conducted to determine which is a better treatment	2	43	1	2.0000	0.6901	2		
H_I think that my participation in the trial will contribute to the benefit to future patients with the same disease	1	185	0	1.4432	0.5694	1	0.00260	0.00756
H_I think that my participation in the trial will contribute to the benefit to future patients with the same disease	2	44	0	1.7500	0.7193	2		
I_I think that my relationship with my doctor will become worse if I refuse to participate in the trial	1	184	1	3.9728	1.1329	4	0.52077	0.77461
I_I think that my relationship with my doctor will become worse if I refuse to participate in the trial	2	44	0	4.0909	0.9104	4		
J_I am worried about the fact that I cannot choose which treatment to receive if I participate in the trial	1	183	2	2.7049	1.3178	3	0.01039	0.00967
J_I am worried about the fact that I cannot choose which treatment to receive if I participate in the trial	2	43	1	2.1395	1.1666	2		
K_I am concerned about leakage of my personal information if I participate in the trial	1	184	1	4.2609	0.9623	5	0.11278	0.09300
K_I am concerned about leakage of my personal information if I participate in the trial	2	44	0	4.0000	1.0343	4		
L_I am concerned about an increased burden on me if I participate in the trial	1	185	0	3.4324	1.1828	3	0.25263	0.31042
L_I am concerned about an increased burden on me if I participate in the trial	2	44	0	3.2045	1.1926	3		
M_I am concerned about the side effects of the treatments used in the trial, if I participate in it	1	184	1	2.1739	1.0361	2	0.07865	0.23363
M_I am concerned about the side effects of the treatments used in the trial, if I participate in it	2	44	0	2.5000	1.3382	2		
S_Do you want to know what questions other patients who received the explanation about this trial asked their doctors?	1	184	1	2.5272	1.1496	2	0.92195	0.61646
S_Do you want to know what questions other patients who received the explanation about this trial asked their doctors?	2	44	0	2.5455	0.9265	3		

Data of FEEL and FEEL II were combined.

Table 3. The results of statistical comparisons of answers to Question Q, N and U

	Participants	Refusers	Sum
(Q) Days spent to make the decision			
1 day	72	8	80
%	38.92	18.18	
3–4 days	39	8	47
%	21.08	18.18	
7 days	47	22	69
%	25.41	50	
10–14 days	19	5	24
%	10.27	11.36	
15 days or more	8	1	9
%	4.32	2.27	
Sum	185	44	229
Missing data = 0			
Chi-square test *P*-value			
0.0168			
(N) The item that affected the decision most ranked No.1in B to M			
B	26	1	27
%	15.85	2.44	
B·F·G·H all	1	0	1
%	0.61	0	
C	12	1	13
%	7.32	2.44	
D	23	1	24
%	14.02	2.44	
E	1	0	1
%	0.61	0	
F	11	1	12
%	6.71	2.44	
G	14	0	14
%	8.54	0	
H	34	0	34
%	20.73	0	
I	1	1	2
%	0.61	2.44	
J	15	14	29
%	9.15	34.15	
L	3	2	5
%	1.83	4.88	
M	23	19	42
%	14.02	46.34	
O	0	1	1
%	0	2.44	
Sum	164	41	205
Missing data = 24			
Chi-square test *P*-value			
<0.0001			
(U) The person who affected the decision ranked No.1			
Your parent(s)/your brother(s)/your sister(s)	3	5	8
%	1.67	11.63	
Your spouse/child(ren)	38	15	53
%	21.11	34.88	
Your friend(s)	3	1	4
%	1.67	2.33	
Your doctor	119	17	136
%	66.11	39.53	
Doctor(s) other than your doctor	3	1	4
%	1.67	2.33	
Nurse(s)/CRC(s)	9	1	10
%	5	2.33	
Other patients who participated in the trial	5	3	8
%	2.78	6.98	
Sum	180	43	223
Missing data = 6			
Chi-square test *P*-value			
0.0045			

Data of FEEL and FEEL II were combined.

Conclusions

To enhance the consent rate in randomized trials of metastatic breast cancer patients, concepts of the trials must be considered important and acceptable not only by patients but also by doctors and their families.

Conflict of interest statement

Dr. Takahashi and Dr. Park report grants from Taiho Pharmaceutical Co., Ltd outside this work. Dr. Mukai and Dr. Takashima reports honoraria from Taiho Pharmaceutical Co., Ltd outside this work. The other authors have nothing to disclose.

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Appendix

Questionnaire

B) My doctor wanted me to participate in this trial.

C) My family or friends wanted me to participate in this trial.

D) I am satisfied with the explanation I received about this trial from my doctor or clinical research coordinator.

E) I am satisfied with the explanation I received about this trial from printed matter.

F) Both treatment regimens used in the trial are suitable to me.

G) I know that the trial is conducted to determine which is a better treatment.

H) I think that my participation in the trial will contribute to the benefit to future patients with the same disease.

I) I think that my relationship with my doctor will become worse if I refuse to participate in the trial.

J) I am worried about the fact that I cannot choose which treatment to receive if I participate in the trial.

K) I am concerned about leakage of my personal information if I participate in the trial.

L) I am concerned about an increased burden on me if I participate in the trial.

M) I am concerned about the side effects of the treatments used in the trial, if I participate in it.

N) What items from B) to M) affected your decision most? Please rank the top three items in the order that they affected your decision.

No. 1 ( ), No. 2 ( ), No. 3 ( ).

O) What is your age?

P) Have you ever received chemotherapy?

Q) How many days did you spend to make your decision after you had received the explanation about the trial?

R) How do you prefer that the decision about your participation is made?

My doctor makes the decision alone.

My doctor makes the decision after he or she confers with me.

My doctor and I make the decision together.

I make the decision after I consult my doctor.

I make the decision alone.

S) Do you want to know what questions other patients who received the explanation about this trial asked their doctors?

T) What side effects of chemotherapy are you concerned about most? Rank the top three according to the order of most serious concern.

1. Myelosuppression (becoming more susceptible to infectious diseases).
2. Hair loss.
3. Fatigue.
4. Joint and/or muscle pain.
5. Peripheral neuropathy (sensory change or numbness of hands and/or feet).
6. Nausea, vomiting, or loss of appetite.
7. Digestive symptoms (diarrhea, constipation etc.)
8. Others ( ).

No. 1 ( ), No. 2 ( ), No. 3 ( ).

U) Whose opinions most affected your decision on whether or not to participate in this trial? Rank the top three according to the order of importance.

1. Your parent(s)/your brother(s)/your sister(s).
2. Your spouse/child(ren).
3. Your friend(s).
4. Your doctor.
5. Doctor(s) other than your doctor.
6. Nurse(s)/CRC(s).
7. Other patients who participated in the trial.
8. Other(s) ( ).

No. 1 ( ), No. 2 ( ), No. 3 ( ).