Research on factors associated with successful phase III trials of new drugs for solid tumors

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Abstract

Background: Phase III trials of new anticancer agents for solid tumors have a low success rate. Based on the most recent comprehensive data, this study investigated factors related to trial design and operation that were associated with the probability of success of phase III trials for solid tumors.

Methods: ClinicalTrials.gov. was used to identify relevant clinical trials started between September 2007 and December 2017. Then, variables related to the selected trials, such as the types of primary endpoint and the patients' enrollment period, were obtained from relevant papers and ClinicalTrials.gov. Based on the collected data, multivariate logistic regression analysis and multivariate linear regression analysis were carried out to identify the factors associated with successful results (Study 1) and patients' enrollment period (Study 2).

Results: In Study 1, 400 phase III trials were found to be eligible, among which 207 were unsuccessful trials and 193 were successful trials. According to the multivariate logistic regression analysis, types of primary endpoint (time to event endpoint other than overall survival [OS] vs. OS), control arm (other vs. strong standard of care [SOC]), start year of the trial (2012–2017 vs. 2007–2011), and patients' enrollment period had a statistically significant relationship with the success. In Study 2, 317 phase III trials were found to be eligible. The median patients' enrollment period was 1.95 years. According to the multivariate linear regression analysis, the following factors had a statistically significant relationship with the patients' enrollment period: features of control arm (comparison with SOC vs. comparison with best supportive care/no treatment/placebo alone in the control arm), study drug class (immune checkpoint inhibitors vs. others (cytotoxic agent etc.) and targeted drugs vs. others), and sponsor

(pharmaceutical company vs. other research organization).

Conclusion: Factors associated with the success of phase III trials of anticancer agents for solid tumors were identified in the present study, which will serve as useful information in investigating the design and operation plans of future clinical trials. Among others, accelerating patients' enrollment would be important so that the initial trial hypothesis will not be affected. It is expected that, based on the findings of this study, more efforts will be made to improve the probability of success of phase III trial for solid tumors from the viewpoints of trial design as well as trial operation, including the measures to shorten patients' enrollment period.

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Abbreviations

BSC	Best supportive care
CI	Confidential interval
CR	Complete response
CTLA4	Cytotoxic T-lymphocyte-associated antigen 4
DFS	Disease free survival
FDA	Food and Drug Association
GI	Gastrointestinal
ICI	Immune checkpoint inhibitor
NA	Not available
NCCN	National comprehensive cancer network
NSCLC	Non-small cell lung cancer
PR	Partial response
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PFS	Progression free survival
SOC	Standard of care

1. Introduction

Many medical needs remain unmet in the field of oncology and competition in the development of new anticancer agents is increasing. For drugs in the field of oncology, long periods of clinical development are required compared with other diseases due to difficulties in recruiting patients, longer time needed to establish efficacy, and low success rates for phase III trials and drug approval [1-3]. In particular, the success rate of drug approval for solid tumors is known to be lower than that for hematological malignancies in the field of oncology [4]. Thus, there could be apprehensions about the increasing development cost and poor development efficiency for solid tumors, which have substantially impacted companies' management.

Previous studies have reported on the phase III trial design factors (biomarker strategy, types of primary endpoint) that are associated with trial result and drug approval [5,6]. Because the trial design is an important factor that affects the success of each trial, these preliminary studies are considerable. However, these reports have limitations such as being descriptive without appropriate statistical methods, targets being mostly targeted drugs, and results being based on univariate analysis. In addition, the trial operation in phase III, other than the main trial design, might be another potential factor affecting the result. There was a review report of phase III trials that targeted first-line non–small-cell lung cancer (NSCLC) with a similar trial design (first-line, monotherapy, control arm of platinum-based chemotherapy, etc.) for the same drug class of anti- Programmed cell death 1 (PD-1) antibodies, nivolumab, and pembrolizumab, where pembrolizumab was successful and nivolumab was not [7]. This may suggest factors other than drugs and the main trial design, such as operation methods, that potentially affects the trial result. In fact, to the best of our knowledge, there has been no study that focused on both trial design and operation method for phase III trials and examined their effects on the trial result. Furthermore, recently, rapid

changes have been seen in the available anticancer agents, with the approval of several immune checkpoint inhibitors, and the environment surrounding the development of anticancer agents has been changing compared to a time when the previous studies were conducted.

The purpose of this study was to comprehensively examine factors related to the results of phase III trials of anticancer agents for solid tumors based on the most recent information, focusing on trial design and operation. This thesis is composed of two studies. In Study 1, factors related to success and unsuccess of phase III trials, which has a significant impact on the approval of new drugs, were investigated. Then, in Study 2, based on the result of Study 1, we focused on the patients' enrollment period, which is a matter that researchers can handle, and investigated factors related to it. Based on the results of the two studies, we discussed and proposed points to focus on when planning future development plans, in particular, toward shortening the patients' enrollment period in the clinical trials.

2. Research on factors associated with successful phase III trials (Study 1)

2.1 Objective

This Study 1 was aimed at investigating factors related to trial design and operation that were closely associated with the probability of success of phase III trials of anticancer agents for solid tumors based on the most recent comprehensive data to provide new knowledge toward improved plan and conduct of future clinical trials.

2.2 Method

Trial selection

ClinicalTrials.gov. was used as the search engine to extract clinical trials from a start date between September 27th, 2007 (registration on ClinicalTrials.gov. has been required for studies that were initiated after September 27, 2007) and December 31st, 2017 (publication of the most recent phase III trial results could be expected) while considering the following conditions—condition or disease: oncology NOT leukemia NOT multiple myeloma NOT lymphoma; study type: interventional studies; study results: all studies; recruitment status: active, not recruiting/completed/terminated; the study phase: phase 3; and study start: from September 27th, 2007 to December 31st, 2017. Additionally, the inclusion criteria indicated in Table 1 was used to select the target trials (randomized phase III trials for patients with solid tumors).

Then, first, the availability of the trial outcome was identified. When phase III trial papers were available through "Publications automatically indexed to this study by ClinicalTrials.gov Identifier" of ClinicalTrials.gov., they were obtained from relevant journals. If the papers were not available through the site, the ClinicalTrials.gov. Identifier

was used to identify relevant papers and abstracts from PubMed and Google Scholar. If there was information that could not be confirmed in the identified papers (including supplemental information) or if papers were not published but trial results and related information could be collected on ClinicalTrials.gov., necessary data was obtained from ClinicalTrials.gov. (including protocols and SAP referenced on Clinicaltrials.gov.). Target trials were further selected based on the exclusion criteria (Table 1).

Table 1. Inclusion and exclusion criteria for trial selection for Study 1

Inclusion criteria	☐	Trials that targeted patients with solid tumors;
	☐	Randomized trials with at least 150 patients; and
	☐	Phase III trials (phase II/III trials are considered phase III trials).
Exclusion criteria	☐	Trials for which the result cannot be obtained;
	☐	Trials that do not involve drug intervention (e.g., surgery, radiation therapy, etc.);
	☐	Trials where the primary endpoint does not include OS or other time-to-event endpoints such as progression free survival (PFS) or disease free survival (DFS);
	☐	Trials on biosimilar or generic drugs; and
	☐	Trials of target patients who do not have solid tumors (precursor diseases and pathologies that lead to cancer).

Definition of variables

Definition of objective variables.

When the primary endpoint of a phase III trial was statistically significant, we considered the trial to be "successful" and when it was not, we considered it to be "unsuccessful." Statistical significance here meant the p value being below the predetermined significance

level. If the predetermined significance level was unknown, significance level of 5% for classification was used. If the p value obtained in the trial was unknown, as long as the result was clear in the published information such as “did not meet primary endpoint,” “no significant difference,” etc., such information was referred to as well.

The standard of success was as follows: if there was a single primary endpoint of either OS or time-to-event endpoint like PFS or DFS other than OS, a statistical significance in the primary endpoint was considered successful, and if there were two or more primary endpoints including OS and other time-to-event endpoints, as long as there was a statistically significant difference in OS, it was considered successful. The standard of unsuccessful was as follows: if there was a single primary endpoint of either OS or time-to-event endpoint other than OS, lack of a statistical significance in the primary endpoint was considered unsuccessful, and if there were two or more primary endpoints including OS and other time-to-event endpoints, lack of a significant difference in OS was considered to indicate unsuccessful.

Definition of explanatory variables.

Factors related to phase III trial design were presence/absence of biomarker strategy identifying subjects with biomarkers, cancer type (gastrointestinal (GI) cancer, NSCLC, breast cancer, other), control arm (SOC [Category 1 in the latest national comprehensive cancer network {NCCN} guidelines], SOC [Category 2A in the latest NCCN guidelines], other [BSC, placebo, or other]), study drug class (ICI, targeted therapy, or other), regimen (monotherapy, combination), and primary endpoint (OS [including OS as a co-primary endpoint], Non-OS [time-to-event endpoint like PFS or DFS other than OS]). Factors related to phase III trial operation were sponsor (other research organizations, pharmaceutical companies), start year of phase III trial (2007–2011, 2012–2017), and patients’ enrollment period (if the available enrollment date was only the month, for convenience, we entered the

first day of the month). Biomarker strategy, cancer type, study drug class, regimen, primary endpoint, and sponsor were selected because they were also used in relevant previous studies [5,6,8]. Control arm, start year of phase III trial, and patients' enrollment period were selected for their possible effect on the phase III outcome and the data availability.

A biomarker strategy meant here that a biomarker was used for selecting targeted populations in the eligibility criteria or in the analysis for the primary endpoint [9,10]. Targeted drug in the study drug class was defined as drugs that block the growth and spread of cancer by interfering with specific molecules (molecular targets) that are involved in the growth, progression, and spread of cancer such as signal transduction inhibitors, apoptosis inducers, and angiogenesis inhibitors [11]. ICI in the study drug class was defined as those blocking immune checkpoint proteins like Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), PD-1, and Programmed cell death ligand 1 (PD-L1).

Statistical methods

First, the number of successful trials and unsuccessful trials were tallied for each category of the explanatory variables, and success rates were calculated. Difference in the success rate among categories was examined using chi-squared test or Mann–Whitney U test depending on the types of data. In addition, we descriptively calculated the overall success rate and the success rate per start year of phase III trial.

To evaluate the relationship of the phase III trial design and operation with the success of phase III trials, we conducted a multivariate logistic regression analysis using the binary outcome (successful or unsuccessful) of the phase III trials as an objective variable and all the phase III trial design and operation factors as explanatory variables. The adjusted odds ratio for each explanatory variable was calculated and factors associated with the success of phase III trials were examined. A *p*-value of less than 0.05 was considered statistically significant.

Considering the impact of missing values on the result, a sensitivity analysis excluding factors with many missing values was also performed. Chi-squared test, Mann–Whitney U test, and logistic regression analysis were performed using EZR on R commander version 1.41, October 1, 2019 [12].

2.2 Results

Trial selection and characteristics

The number of trials identified through the data extraction on October 10, 2019 via ClinicalTrials.gov was 2,085. Among these trials, 902 trials were chosen through the inclusion criteria. After considering the exclusion criteria, 400 trials were selected for the analysis—207 unsuccessful trials and 193 successful trials (Fig. 1). The selected trials are considered as completed phase III trials for solid cancers with fairly good trial design and reliable trial outcome. The overall success rate was 48.3%. When divided by the start year of phase III trial, the success rate was approximately 30%–40% between 2007 and 2011, whereas it was approximately 50%–70% between 2012 and 2017 (Fig. 2).

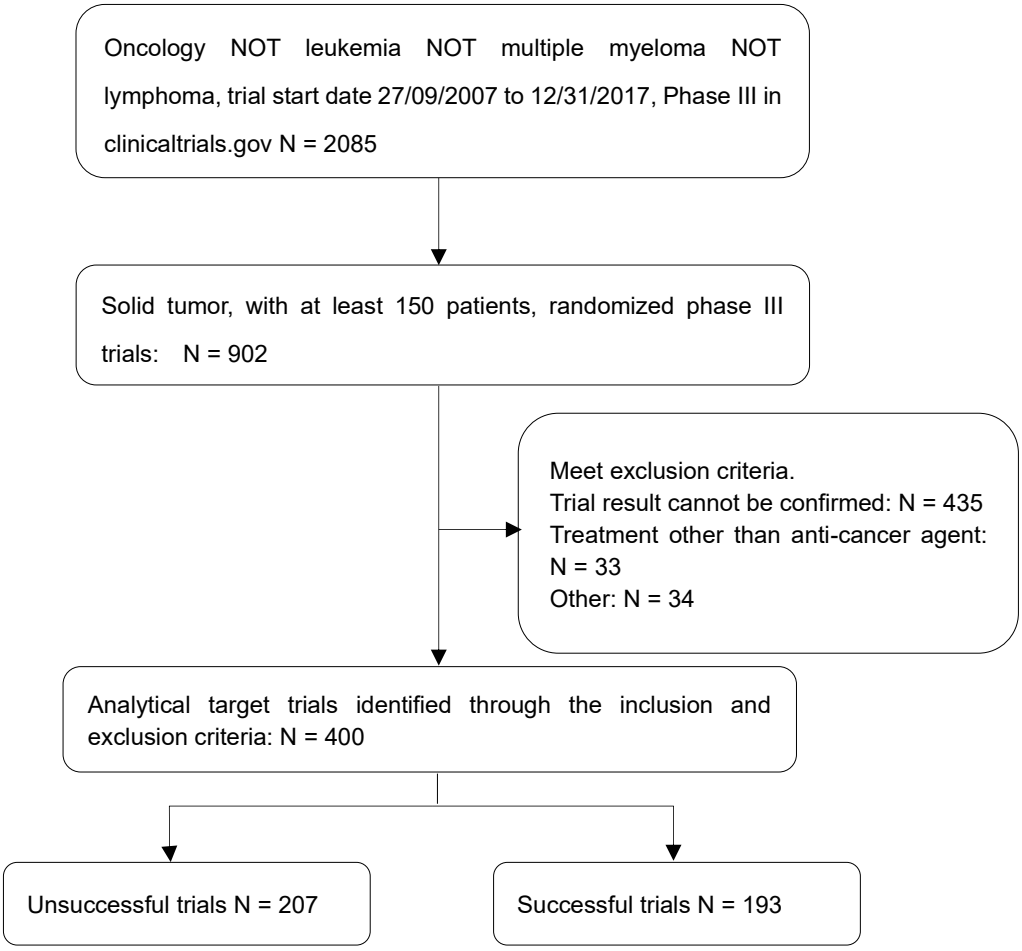


Fig 1. Flow diagram of the trial selection for Study 1

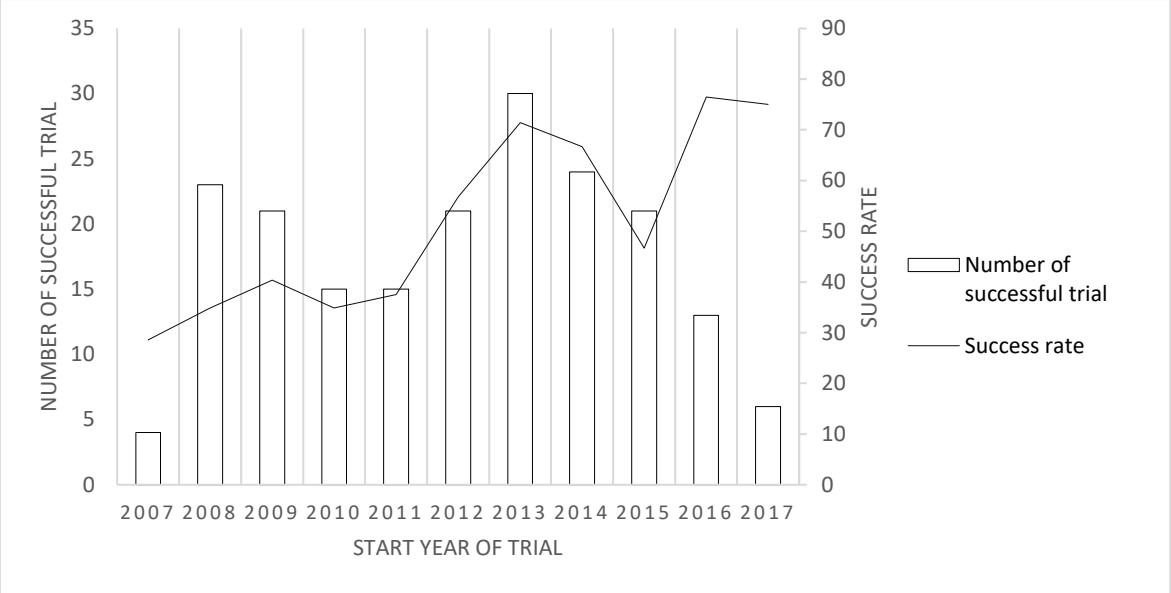


Fig 2. Number of successful trial and success rate by the start year of phase III trial

Imbalance was observed for characteristics excluding the study drug class between the groups of successful and unsuccessful phase III trials. For the patients' enrollment period, the median for successful trials was 1.73 years, which was about 0.74 years shorter than that for unsuccessful trials (Table 2). Missing values were only confirmed in the patients' enrollment period, and the rate of missing values was 14.8% (59/400).

Table 2. Characteristics of the trials for Study 1

Categorical variable	Number of unsuccessful trials (%) N = 207	Number of successful trials (%) N = 193	Success rate	*p*-value
Biomarker strategy (%)				
NO	167 (80.7)	129 (66.8)	43.6%	0.002
YES	40 (19.3)	64 (33.2)	61.5%	
Cancer type (%)				
GI cancer	67 (32.4)	39 (20.2)	36.8%	0.043
NSCLC	37 (17.9)	39 (20.2)	51.3%	
Breast cancer	26 (12.6)	34 (17.6)	56.7%	
Other[a]	77 (37.2)	81 (42.0)	51.3%	
Control arm (%)				
Strong SOC	66 (31.9)	33 (17.1)	33.3%	<0.001
SOC	91 (44.0)	85 (44.0)	48.3%	
Other[b]	50 (24.2)	75 (38.9)	60.0%	
Study drug class (%)				
ICI	31 (15.0)	34 (17.6)	52.3%	0.184
Targeted drug	98 (47.3)	103 (53.4)	51.2%	
Other	78 (37.7)	56 (29.0)	41.8%	
Regimen (%)				
Mono	66 (31.9)	94 (48.7)	58.8%	0.001
Combo	141 (68.1)	99 (51.3)	41.3%	
Primary endpoint (%)				
OS[c]	131 (63.3)	74 (38.3)	36.1%	<0.001

Categorical variable	Number of unsuccessful trials (%) N = 207	Number of successful trials (%) N = 193	Success rate	*p*-value
Non-OS[d]	76 (36.7)	119 (61.7)	61.0%	
Sponsor (%)				
Pharmaceutical company	152 (73.4)	165 (85.5)	52.0%	0.004
Other research organization	55 (26.6)	28 (14.5)	33.7%	
Start year of phase III trial (%)				
2007–2011	137 (66.2)	78 (40.4)	36.3%	<0.001
2012–2017	70 (33.8)	115 (59.6)	62.2%	
Numerical variable	Median patients' enrollment period for unsuccessful trials (Min, Max) N = 162	Median patients' enrollment period for successful trials (Min, Max) N = 179		
Patients' enrollment period (year)	2.47 (0.48, 7.67)	1.73 (0.36, 9.25)	-	<0.001

[a] Approximately 20 cancer types were included in the category of "other". The main cancer types categorized as "other" were prostate cancer (33 trials), melanoma (25 trials), ovarian cancer (20 trials), renal cell carcinoma (14 trials), and head and neck cancer (13 trials).

[b] Best supportive care, Placebo, less than category 2A in NCCN guidelines

[c] including OS as the co-primary endpoint

[d] time-to-event endpoint other than OS (e.g., PFS etc)

GI: Gastrointestinal, NSCLC: Non–small cell lung cancer, SOC: Standard of care, ICI: Immune checkpoint inhibitor, OS: Overall survival

Results of logistic regression analysis

The adjusted odds ratio for each factor through multivariate logistic regression analysis was calculated. Factors that presented statistical significance were control arm (other vs. strong SOC) (odds ratio [OR]: 3.06 [1.39–6.73], p = 0.0053), primary endpoint (Non-OS vs. OS) (OR: 2.79 [1.59–4.89], p < 0.001), start year of phase III trial (2012–2017 vs. 2007–2011) (OR: 3.28 [1.87–5.77], p < 0.001), and patients' enrollment period (OR: 0.77 [0.60–0.99], p = 0.040) (Table 3).

Table 3. Result of multivariate logistic regression analysis

Factor	Reference		Odds ratio (95% CI)	*p*-value
Biomarker strategy	NO	YES	1.19 (0.62, 2.26)	0.60
Cancer Type	GI	NSCLC	1.58 (0.73, 3.46)	0.25
		Breast Ca	1.43 (0.58, 3.54)	0.44
		Other	1.34 (0.69, 2.61)	0.38
Control arm	Strong SOC	SOC	1.63 (0.85, 3.15)	0.14
		Other	3.06 (1.39, 6.73)	0.0053*
Study drug class	ICI	Targeted Drug	0.67 (0.28, 1.63)	0.38
		Other	0.90 (0.36, 2.28)	0.83
Regimen	Mono	Combo	0.96 (0.52, 1.79)	0.91
Primary endpoint	OS[a]	Non-OS[b]	2.79 (1.59, 4.89)	<0.001*
Sponsor	Other research organization	Pharmaceutical company	1.28 (0.63, 2.62)	0.50
Start year of phase III trial	2007–2011	2012–2017	3.28 (1.87, 5.77)	<0.001*
Patients' enrollment period	-	-	0.77 (0.60, 0.99)	0.040*

*Statistically significant (P <.05)

[a]including OS as the co-primary endpoint, [b]time-to-event endpoint other than OS

GI: Gastrointestinal, NSCLC: Non–small-cell lung cancer, SOC: Standard of care, ICI: Immune checkpoint inhibitor, OS: Overall survival, CI: Confidence interval

Results of sensitivity analysis

A multivariate logistic regression analysis by excluding the factor of patients' enrollment period, in which missing values were confirmed in 14.8% of data, was conducted as a sensitivity analysis. Primary endpoint, control arm, and start year of phase III trial, which presented a significant relationship with the probability of success in the main analysis, were also significant in the sensitivity analysis, showing consistency (Table 4).

Table 4. Result of multivariate logistic regression analysis (excluding factors of "patients' enrollment period")

Factor	Reference		Odds ratio (95% CI)	*p*-value
Biomarker strategy	NO	YES	1.26 (0.71, 2.22)	0.43
Cancer Type	GI	NSCLC	1.44 (0.73, 2.87)	0.30
		Breast Ca	1.26 (0.57, 2.81)	0.57
		Other	1.19 (0.66, 2.17)	0.56
Control arm	Strong SOC	SOC	1.62 (0.89, 2.94)	0.11
		Other	2.50 (1.24, 5.05)	0.010*
Study drug class	ICI	Targeted drug	0.96 (0.46, 2.01)	0.92
		Other	1.01 (0.47, 2.17)	0.97
Regimen	Mono	Combo	0.76 (0.44, 1.31)	0.32
Primary endpoint	OS[a]	Non-OS[b]	2.78 (1.67, 4.62)	<0.001*
Sponsor	Other research organization	Pharmaceutical company	1.39 (0.76, 2.54)	0.29
Start year of phase III trial	2007–2011	2012–2017	3.05 (1.84, 5.05)	<0.001*

*Statistically significant (P < .05)

[a]including OS as the co-primary endpoint, [b]time-to-event endpoint other than OS

NSCLC: Non–small-cell lung cancer, GI: Gastrointestinal, SOC: Standard of care, ICI: Immune checkpoint inhibitor, OS: Overall survival, CI: Confidence interval

2.3 Discussion

In this study, the overall success rate of phase III trials of anticancer agents was 48.3%. In previous studies, it was reported to be 40%–50% [1,3,8], and our finding is consistent with these results. However, in this study, the success rate increased since 2012. The results of unsuccessful trials are not often published compared with those of successful trials; it was reported that in a previous study, 60% of unsuccessful trials were not published [13]. Alternatively, even when the trial results are published, there might be a delay until publication, resulting in a period of 2–3 years between the completion of a trial and publication. In particular, the time from trial completion to publication of unsuccessful trials was 1.3 years later than the time of successful trials [14,15]. Therefore, such publication bias may be a reason for the apparently different success rates between the years 2007–2011 (30%–40%) and 2012–2017 (50%–70%) for the analytical target trials. Even if this bias exists, we included "start year of phase III trial" as an explanatory variable in the multivariate logistic regression analysis to adjust the OR.

Shorter patients' enrollment period was associated with successful phase III in this study. It is known that many factors play a role in low rates of trial participation such as financial barriers, lack of resources, uncertainty of risk-benefit ratio, and types of control arm [16,17,18]. Operational factors such as the number of trial sites, which is a controllable factor, might also affect the patients' enrollment period. In addition, the result of trials in the prior phase might affect it. For example, higher response rate or other attractive efficacy data in the previous phase might lead to investigators' and patients' higher motivation for patients' enrollment. These might be confounding factors to this outcome. Although there could be many confounding factors, it is of great

significance to actively consider and accelerate the enrollment so that the external medical environment such as approval of new subsequent therapy would not affect the original trial hypothesis. Accelerating enrollment is also useful in terms of getting innovative drugs and new indications to patients faster.

The type of primary endpoint was reported to be associated with the results of phase III trials in previous studies [3,6,14]. And in the present study, it was also a significant factor, both in the multivariate logistic regression analysis and the exploratory sensitivity analysis. This result would be generalized and show that trials tend to be unsuccessful when OS is set as a primary endpoint. OS is known to be easily influenced by subsequent treatment due to treatment switching in patients that were originally in the control arm [19]. This may be one of the reasons that OS as a primary endpoint was associated with unsuccessful phase III results. A trial design that has a time-to-event endpoint other than OS, such as PFS, would be preferable based on this study's result. However, when using an endpoint such as PFS, particularly in an open-label trial, an evaluation bias could exist. Moreover, it may not correlate to OS, the most reliable endpoint for evaluating anticancer agents [16]. When using only a time-to-event endpoint other than OS as the primary endpoint, a strategy to resolve or mitigate such problems and disadvantages is necessary. Evaluating OS as a key secondary endpoint might be an option. At the same time, we need to deepen our understanding as to the correlation between surrogate endpoints and OS.

In this study, we confirmed that trials using a control arm of placebo, BSC, or drug with lower evidence level were associated with a high probability of success compared with trials using a control arm of strong SOC. Unmet medical needs are expected to be higher in disease areas where there is no established standard therapy or where existing

medications have a low evidence level. The result of the present study would encourage development of new medications in those areas. There are a limited number of treatments in disease areas with small number of patients such as rare cancers [20]. Also, available treatments are limited in highly heterogeneous types of cancer including those being resistant to conventional chemotherapy. It might be meaningful to explore the possibility of using real world data as historical control data in the development of new therapies for rare cancers, which have a particularly low incidence, and to consider a trial design using biomarkers to select patient populations in order to easily show a clinically significant difference in highly heterogeneous types of cancer.

Although the type of primary endpoint and control arm were identified as factors associated with the probability of success in phase III trials, they should be selected based on individual drug's characteristics and expected clinical positioning. The results of the present study should be referred as exploratory data for considering phase III trial design for solid tumors.

Previous studies have identified the biomarker strategy as a factor that is related to the result of phase III trials. However, it was not significant in this study. In previous studies, targeted drugs were the main target, and conclusions were made based on a univariate analysis without adjusting for relevant confounding factors [5,6]. This study comprehensively considered a variety of study drug classes and utilized a multivariate logistic regression analysis. These may be the reasons for differences in the results. A biomarker strategy is an important approach to understand drug characteristics and improve its efficacy. In fact, in a meta-analysis of registration trials of anticancer agents approved by Food and Drug Administration (FDA) and that of oncology phase I and phase II trials, it was reported that higher overall response rate and longer PFS was

expected with a biomarker strategy and many drugs have been approved for patients in whom effects are anticipated based on biomarkers [9,21–23]. Thus, the said strategy was not denied. We need to further investigate the outcome of biomarker strategy in the future.

Limitations of this study were as follows. First, not all trial results during the target period were published and our result could likely be affected by publication bias. Second, evaluation of the evidence level of the control arm was based on the most recent NCCN guidelines rather than those available at the start of each trial. In addition, it is highly likely that there could be unknown confounding factors affecting the phase III outcome and consequently the results of the present study. Further studies are needed to clarify these issues.

3. Research on factors associated with the patients' enrollment period (Study 2)

3.2 Background and objective

In Study 1, a shorter patients' enrollment period was identified as a factor associated with successful phase III trials [24]. Shorter patients' enrollment period would lead to reducing the period of clinical trial itself. It has been also noted that if a new drug is approved during an ongoing phase III trial and used as a subsequent treatment for subjects in the trial, the survival outcome would be affected [19]. Therefore, a shorter patients' enrollment period would help to mitigate the impact of such changes in the external medical environment. It has also been reported that the primary reason for clinical trials' not being completed is a failure to complete enrollment [25]. This is another reason why the patients' enrollment should be prioritized.

In a previous study, it was pointed out that uncertainty about the risk-benefit ratio of a new investigational drug based on prior trials might impact the patients' enrollment in the following trial [16]. Better efficacy outcomes obtained in clinical trials in prior phase may have a better effect on patients' enrollment. Other potential barriers to patients' enrollment include the presence of placebo or no treatment group in the control arm, poor finances and other economic conditions, a lack of resources, patients' feelings, and complexity and rigor of trial design [16, 26]. From the standpoint of trial

operation, the number of subjects, trial sites, and participating countries may influence the patients' enrollment. As an external factor, prevalence of the target disease may also affect it. However, no previous study has comprehensively investigated these factors based on the most recent available data.

Against such a background, this Study 2 was conducted to examine factors associated with patients' enrollment period in phase III trials of new anticancer agents for solid tumors with the aim of exploring the impact of prior phase efficacy results as well as trial design and operation, and external environment on patients' enrollment.

3.3 Method

Trial selection

ClinicalTrials.gov was used as the search engine to extract clinical trials started between September 27th, 2007 (registration on ClinicalTrials.gov is required for studies initiated after September 27th, 2007) and December 31st, 2017 (publication of the most recent phase III trial results could be expected) while considering the following conditions—condition or disease: oncology NOT leukemia NOT multiple myeloma NOT lymphoma; study type: interventional studies; study results: all studies; recruitment status: active, not recruiting/completed/terminated; the study phase: phase III; and study start: from September 27th, 2007, to December 31st, 2017. Additionally, the inclusion criteria indicated in Table 5 was used to select the target trials (randomized

phase III trials for patients with solid tumors). Then, the target trials were further selected based on the exclusion criteria (Table 5).

Table 5. Inclusion and exclusion criteria for trial selection for Study 2

Inclusion criteria	☐ Trials that targeted patients with solid tumors; ☐ Randomized trials with at least 150 patients; and ☐ Phase III trials (phase II/III trials are considered phase III trials).
Exclusion criteria	☐ Trials enrollment data cannot be obtained; ☐ Published papers of phase 3 trials cannot be obtained; ☐ Trials that do not involve drug intervention (e.g., surgery, radiation therapy, etc.); ☐ Trials where the primary endpoint does not include OS or other time-to-event endpoints, such as PFS or DFS; ☐ Trials other than verifying superiority of efficacy; ☐ Trials on biosimilar or generic drugs; and ☐ Trials on target patients who do not have solid tumors (precursor diseases and pathologies that lead to cancer).

Definition of variables

Definition of objective variables

In this Study 2, the patients' enrollment period in phase III trials was defined as an objective variable.

Definition of explanatory variables

In Table 6, factors related to feature of prior phase efficacy outcome were

summarized.

Table 6. Definition of factors related to features of prior phase efficacy outcome

Category	NOTE
Low expectation	The efficacy result in the prior trial was negative (e.g., negative efficacy result for the primary objective in a randomized trial, overall response rate (ORR) < 41% in a single-arm trial, or not available (NA)
High expectation	The efficacy result in the prior trial was positive and ORR ≤ 59% in a randomized trial, or ORR 41-59% in a single-arm trial
Particularly high expectation	The efficacy result in the prior trial was positive and ORR ≥ 60% in a randomized trial, or ORR ≥ 60% in a single-arm trial

The positive result for the primary objective in efficacy in the prior phase was confirmed based on the positive narratives, such as "primary endpoint met," "significant outcome," and "improved outcome," in the Conclusion and Result section of the prior phase trial paper. The negative result in efficacy in the prior phase was judged based on the negative narratives in the Conclusion and Results section of the paper. NA was applied if no efficacy result was available or could not be confirmed in the prior phase trial paper. If the primary efficacy results were both positive and negative in two or more prior trials, then positive result was prioritized. For anticancer drugs approved by the FDA based on ORR, the median ORR was reported to be 41% [27]. We set the threshold 41% with reference to it. Increase in ORR by 20% was supposed to be clinically significant, a threshold of 60% was set as a part of the definition of particularly high expectation.

Other explanatory variables that may be related to the patients' enrollment period were selected from the perspectives of trial design, external environment, and trial operation. Features of control arm (SOC, SOC [confirmatory of add-on efficacy], BSC/No treatment/placebo alone), study drug class (ICI, targeted drugs, others [cytotoxic agent etc.]), and double-blinded design (No, Yes) were factors related to trial design. These explanatory variables related to trial design were selected because they were known as potential factors in the previous studies [26]. A factor related to the external environment was cancer prevalence (major cancer, minor cancer). The number of countries participating in the trial (two or more countries, one country), sponsor (pharmaceutical company, other research organization), and the number of subjects per investigational site (numerical variable) were factors related to trial operation. These external environment and operation factors were selected for their possible effect on the patients' enrollment and the data availability. Among them, sponsor was selected because poor finances conditions and a lack of resources of organization are known as factors related to patients' enrollment [16].

Method for collecting variables

Method for collecting objective variables

The patients' enrollment period was obtained from the publications of the phase III trial. The patients' enrollment period was to be completed by day and month. If there was no data on a particular day of the month, the first day of the month was used as a placeholder.

Method for collecting explanatory variables

Some explanatory variables were obtained using a novel method, as detailed in the table given below (Table 7). Other explanatory variables were obtained simply by reading the relevant phase III trial paper or Clinicaltrials.gov. (e.g. sponsor).

Table 7. Method of collection for explanatory variables

Types of explanatory variables	Method
Features of prior phase efficacy outcome	☐ If more than one prior phase results were cited, the data was primarily collected as follows: (1) positive result in a randomized trial, (2) result of same administration used in the phase III trial, (3) result with the highest response rate, and (4) result of the same tumor types studied in the phase III trial ☐ If the article describes the number of complete response (CR) or partial response (PR) with the evaluable population but does not specify the response rate, the temporary response rate (to 1 decimal point) obtained by dividing (CR + PR) by the evaluable population was used.
Number of subjects per site	The value in the paper was used. If it was not available, the data from Clinicaltrials.gov. was used.
Cancer prevalence (major vs. minor)	☐ It was obtained from the SEER*Stat software version 8.3.8 (http://seer.cancer.gov/resources/). If it was not available, incidence in various publications was referred to. ☐ For the minor cancer, the definition of rare cancer (those with an incidence of <6 cases per 100,000) by the International Rare Cancers Initiative (http://www.irci.info/) was used. [28]

Statistical methods

First, descriptive statistics were calculated for the features of each variable. Kruskal-Wallis test was used to compare the patients' enrollment period among the categorical variables.

To evaluate the relationship between the patients' enrollment period and each explanatory variable, a multivariate linear regression analysis was performed using the

period (numerical outcome) as an objective variable and all the explanatory variables. The adjusted regression coefficient for each explanatory variable was calculated, and factors associated with the patients' enrollment period were investigated. Log-transformed numerical variables from the objective and explanatory variables were used in this analysis. A *p*-value of less than 0.05 was considered statistically significant.

As an exploratory analysis, the relationships between the trial results in the prior phase and the patients' enrollment period were examined using box plots to determine the degree of variation in the patients' enrollment period among each category factor of efficacy result in the prior phase. Considering the impact of different categorizations of efficacy results in the prior phase, sensitivity analyses were performed using the explanatory variable categories of efficacy results of the prior phase as "high + particularly high expectation vs. low expectation" and "particularly high expectation vs. low + high expectation".

Kruskal-Wallis test and linear regression analysis were conducted using EZR on R commander version 1.41, October 1st, 2019 [12].

Table 8. Definition of categories for features of prior phase efficacy outcome for sensitivity analysis #1

Category	NOTE
Low expectation	Efficacy results other than those categorized as high or particularly high expectation (e.g., negative efficacy results for the primary objective in a randomized trial, ORR <41% in a single-arm trial, or NA)
High + particularly high expectation	Efficacy results in the prior phase were positive in a randomized trial, or ORR ≥ 41% in a single-arm trial

Table 9. Definition of categories for features of prior phase efficacy outcome for sensitivity analysis #2

Category	NOTE
Low + high expectation	Efficacy results other than those categorized as particularly high expectation
Particularly high expectation	Efficacy results in the prior phase were positive and ORR ≥ 60% in a randomized trial, or ORR ≥ 60% in a single-arm trial

3.3 Results

Trial selection and characteristics

The number of trials identified through the data extraction on October 10th, 2019 through ClinicalTrials.gov was 2,085. Among these trials, 902 trials were chosen through the inclusion criteria. After considering the exclusion criteria, 317 trials were selected for the analysis (Fig. 3). The selected trials were regarded as completed phase III trials for solid tumors with fairly good trial design and reliable trial outcomes.

The median patients' enrollment period was 1.95 years. Imbalance was observed for features of each categorical factor, such as study drug class, the number of countries participating, and sponsor (Table 10). The median number of subjects per investigational site was 5.15 (Table 11).

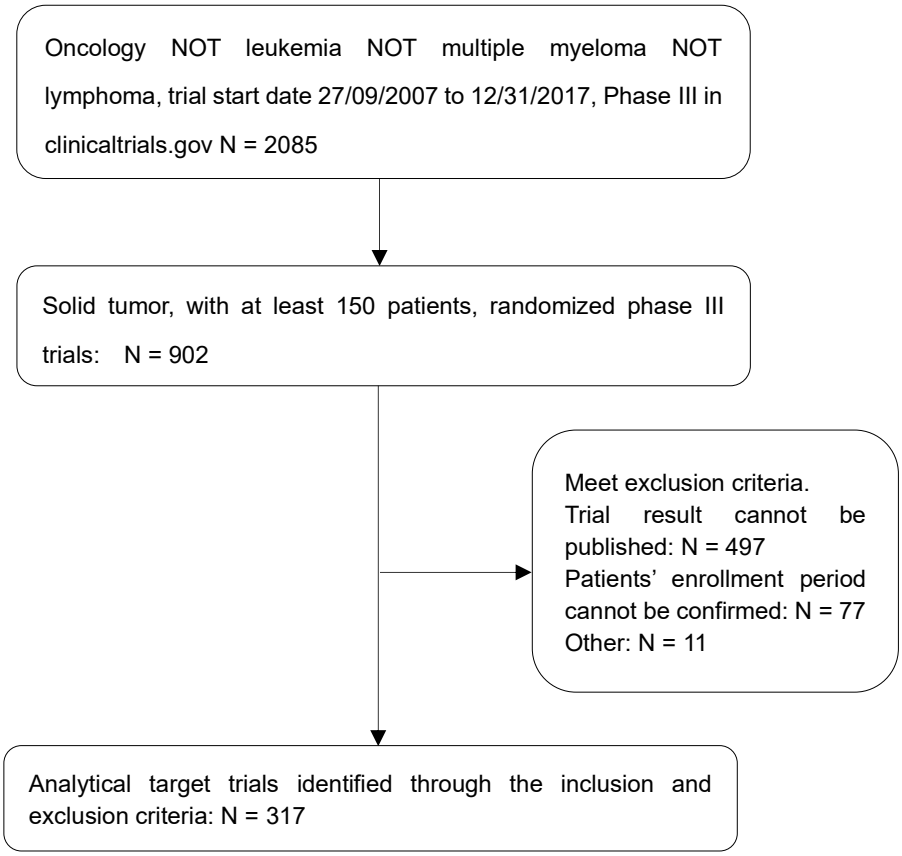


Fig 3. Flow diagram of the trial selection for Study 2

Table 10. Characteristics of the trials for categorical variables for Study 2

Factor	Explanatory variable	Number of data (%)	Median patients' enrollment period [Min, Max]	*p*-value
Overall	-	317	1.95 [0.36, 9.25]	-
Features of prior phase efficacy results	Low expectation	139 (43.8)	1.92 [0.48, 9.25]	0.679
	High expectation	126 (39.7)	2.02 [0.36, 7.80]	
	Particularly high expectation	52 (16.4)	1.96 [0.67, 4.61]	
Features of control arm	Comparison with BSC/No treatment/Placebo alone	61 (19.2)	1.92 [0.62, 5.39]	0.056
	Comparison with SOC	123 (38.8)	1.82 [0.36, 9.25]	
	Comparison with SOC (confirmatory of add-on effect)	133 (42.0)	2.05 [0.67, 7.80]	
Study drug class	Others (cytotoxic agent etc.)	104 (32.8)	2.50 [0.89, 9.25]	<0.001
	ICI	46 (14.5)	1.21 [0.36, 3.84]	
	Targeted drugs	167 (52.7)	1.92 [0.58, 5.90]	
Double blinded design	Yes	152 (47.9)	1.92 [0.36, 4.77]	0.153
	No	165 (52.1)	2.00 [0.45, 9.25]	
Cancer prevalence	Minor cancer	57 (18.2)	2.08 [0.62, 7.80]	0.296
	Major cancer	256 (81.8)	1.92 [0.36, 9.25]	
Number of counties participating	1 country	55 (17.4)	2.92 [0.67, 9.25]	<0.001
	2 countries or more	261 (82.6)	1.84 [0.36, 7.80]	
Sponsor	Other research organization (Academia etc.)	61 (19.2)	3.25 [0.90, 9.25]	<0.001
	Pharmaceutical company	256 (80.8)	1.79 [0.36, 4.77]	

BSC: Best Supportive Care, SOC: Standard of Care, ICI: Immune Checkpoint Inhibitors

Table 11. Characteristics of the trials for numerical variable for Study 2

Numerical viable	Median [Min, Max]
Number of subjects per site	5.15 [0.53, 256.00]

Multivariate linear regression analysis was performed to calculate the regression coefficient for each factor. Features of control arm (comparison with SOC vs. comparison with BSC/no treatment/placebo alone in the control arm) (coefficient [95% CI]: −0.09 [−0.16, −0.01], $p = 0.022$), study drug class (ICI vs. others, and targeted drugs vs. others) (−0.24 [−0.31, −0.17], $p < 0.001$, and −0.10 [−0.15, −0.05], $p < 0.001$), and sponsor (pharmaceutical company vs. other research organization) (−0.22 [−0.28, −0.15], $p < 0.001$) were factors associated with a shorter patients' enrollment period with statistical significance (Table 12).

Table 12. Result of multivariate linear regression analysis for Study 2

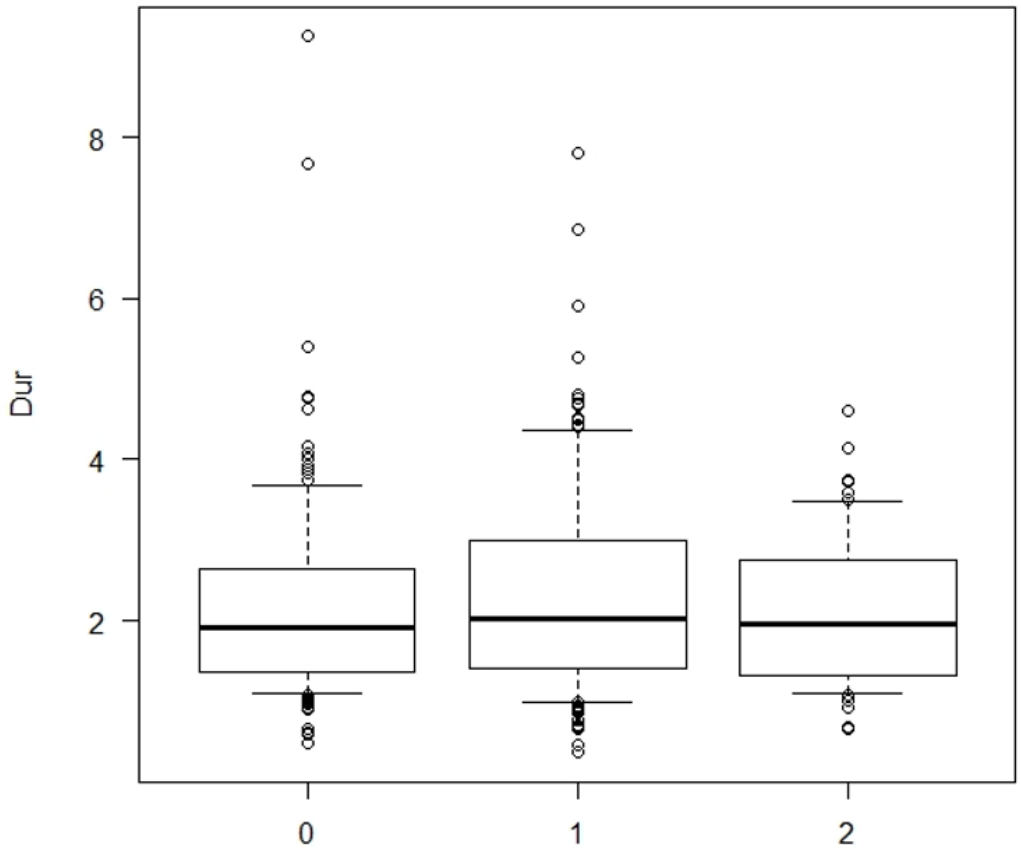
Reference	Factors	Coefficient (95% CI)	*p*-value
Features of prior phase efficacy results: Low expectations	High expectations	0.01 (−0.03, 0.06)	0.64
	Particularly high expectations	−0.02 (−0.08, 0.04)	0.50
Features of control arm: Comparison with BSC /No treatment/Placebo alone	Comparison with SOC	−0.09 (−0.16, −0.01)	0.022*
	Comparison with SOC (confirmatory of add-on effect)	−0.01 (−0.07, 0.05)	0.75
Study drug class: Others (cytotoxic agent etc.)	ICI	−0.24 (−0.31, −0.17)	<0.001*
	Targeted drugs	−0.10 (−0.15, −0.05)	<0.001*
Double blinded design: Yes	No	0.04 (−0.02, −0.09)	0.21
Characteristics of cancer prevalence: Minor cancer	Major cancer	−0.03 (−0.08, 0.02)	0.28
Number of counties participating: 1 country	2 countries or more	0.01 (−0.06, 0.09)	0.72
Sponsor: Other research organization (Academia etc.)	Pharmaceutical company	−0.22 (−0.28, −0.15)	<0.001*
-	Number of subjects per site	−0.03 (−0.12, 0.05)	0.46

*Statistically significant (P < .05)

BSC: Best Supportive Care, SOC: Standard of Care, ICI: Immune Checkpoint Inhibitors

A box plot was created to confirm the degree of variability in the patients' enrollment period among the different categorization of efficacy results in the prior phase (Fig. 4). There was no discernible difference between the categories of low, high, and particularly high expectation.

Sensitivity analyses were performed to ensure that the results of linear regression analysis did not change among the different categorization of efficacy results in the prior phase. Features of control arm, study drug class, and sponsor, which were found to have a significant relationship with the patients' enrollment period in the main primary analysis, were also significant in the sensitivity analysis, indicating consistency (Table 13).



0: Low expectation, 1: High expectation, 2: Particularly high expectation

Dur: patients' enrollment period (year)

Fig 4. Box plot of each different category of prior phase efficacy result

Table 13. Results of multivariate linear regression analysis for each category of efficacy features of the prior phase

Reference	Factor	Sensitivity analysis			
		Efficacy features (high +particularly high vs. low)		**Efficacy features (particularly high vs. low + high)**	
		Coefficient	*p*-value	Coefficient	*p*-value
Features of prior phase efficacy results: Low expectation	High + particularly high expectation	0.00 (-0.04- 0.04)	0.92	-	-
Features of prior phase efficacy results: Low + high expectation	Particularly high expectation	-	-	-0.03 (-0.08- 0.03)	0.36
Features of control arm: comparison with BSC /no treatment/placebo alone	Comparison with SOC	−0.09 (−0.16–0.02)	**0.015***	−0.08 (−0.16–0.01)	**0.023***
	Comparison with SOC (add-on effect)	−0.01 (−0.07–0.05)	0.69	−0.01 (−0.07–0.05)	0.77
Study drug class: others (cytotoxic agent, etc.)	ICI	−0.24 (−0.31–0.17)	**<0.001***	−0.24 (−0.31–0.18)	**<0.001***
	Targeted drugs	−0.10 (−0.15–0.05)	**<0.001***	−0.10 (−0.15–0.05)	**<0.001***
Double-blinded design: Yes	No	0.04 (−0.02–0.09)	0.21	0.04 (−0.02–0.09)	0.21
Cancer prevalence: minor cancer	Major cancer	−0.03 (−0.08–0.03)	0.31	−0.03 (−0.08–0.03)	0.31
Number of counties participating: 1 country	2 countries or more	0.01 (−0.06–0.09)	0.71	0.01 (−0.06–0.09)	0.7
Sponsor: other organization (academia, etc.)	Pharmaceutical company	−0.22 (−0.28–0.15)	**<0.001***	−0.22 (−0.28–0.15)	**<0.001***
-	Number of subjects per site	−0.03 (−0.12–0.05)	0.45	−0.03 (−0.12–0.06)	0.48

*Statistically significant (P < .05)

BSC, best supportive care; SOC, standard of care; ICI, immune checkpoint inhibitors

3.4 Discussion

In Study 2, features of the control arm (comparative studies with standard therapies) and study drug classes (ICIs or Targeted drugs) were shown to be related to the shorter patient's enrollment period. Expectation of investigators and patients for the trial design that active treatments would be used in both arms, and investigational drugs of a single agent or a combination regimen which outweigh the standard of care, may increase their motivation to enroll/participate in the trial and contribute to the shorter enrollment period. On the other hand, the feature of control arm that examined add-on effect to a SOC compared with BSC/no treatment/placebo alone did not show statistically significant association in the present study. There is a report that the risk-benefit ratio of a new investigational drug obtained from preceding trials affects the patients' enrollment [16], and in a trial to verify the add-on effect to a standard drug, not only the additive effect of the investigational drug but also the concern about the additional toxicity may affect the patients' enrollment period. In addition, expectations of physicians and patients about the novel mechanism of action of ICIs and targeted drugs may have contributed to the shortening. Patient's perceptions of personal benefit or "benefit for me" have been found to be the best predictors of participation in clinical trials [29,30]. Results of the present study for the control arm (SOC) features and the

study drug classes (ICI or targeted drug) were considered consistent with this.

In the present study, sponsor (pharmaceutical company) was identified as a factor related to the shorter patients' enrollment period. Financial barriers and a lack of resources for patients and physicians to support clinical trial enrollment have been reported to have an impact on patients' enrollment in a previous study [16]. In general, pharmaceutical companies have more financial and human resources than other research organizations, such as academia, which may have influenced the shortening of the enrollment period. Therefore, a major issue remains in clinical trials conducted by organizations other than pharmaceutical companies. In terms of economic perspective when organizations other than pharmaceutical companies execute clinical trials, the reality is that there are few practical solutions to overcome the obstacles [16]. However, there would be some potential solutions to this. In addition to conventional funding such as government assistance and collaboration with pharmaceutical companies, new frameworks, such as crowdfunding may be one of the potential solutions. In terms of resource perspective, one solution would be to strengthen cooperation among research organizations in each country and to create a framework that allows for larger-scale research activities on a global scale to reduce human resources. Furthermore, another solution would be to design data management using electronic medical records and

unified networks to reduce human resources. Regardless of sponsor type, it is also important to work on patients' enrollment planning and trial design based on "patient-focused" principles so that the patients' voice and engagement are incorporated into the protocol and the informed consent form [31]. This would increase the patients' enrollment while reducing the burden of patient participation in clinical trials. This approach needs to be more considered in clinical trials sponsored by organizations other than pharmaceutical companies.

Since "benefit for patients" has been reported as a factor influencing patients' enrollment [30], it is considered that the magnitude of the expected benefit due to the efficacy shown in the prior phase could influence patients' enrollment. However, its relationship with the enrollment period was not indicated in either the primary or sensitivity analyses. Given that large-scale phase III trials usually start with a good benefit-risk balance information for the investigational drug and that many physicians and patients are motivated to participate in the trials based on such information, the efficacy results from the prior phase are less likely to affect the enrollment period.

Limitations of Study 2 were similar to those of Study 1. First, because not all trial results were published during the target period, our findings may have been influenced by publication bias (e.g. unsuccessful phase III results are less likely to be published

than successful results). Second, although the robustness of the data was confirmed by sensitivity analyses based on different categorization of efficacy data for prior phase results, exact development strategies and data up to prior phases were unknown because only published information was used for this study. Furthermore, it is highly likely that unknown confounding factors (such as competitors' clinical status and safety characteristics of investigational drugs) influenced the patients' enrollment period and consequently the results of the present study.

4. Overall Discussion

First, I would like to discuss what we should focus on for successful phase III trials for solid tumors. In this study, several factors were identified by multivariate analysis based on the most recent available and comprehensive data. Among them, shortening of patients' enrollment period was identified as a factor related to the success of the phase III trials, which is a novel finding. It is critical because shortening of patients' enrollment period increases the possibility of verifying efficacy of the investigational drug in the same environment as the initial hypothesis. Also, from the viewpoint of delivering innovative drugs and new indications to patients sooner, it is considered to be beneficial to promote trial enrollment.

Another point to be discussed is the relationship between the motivation of investigators as well as patients and the patients' enrollment period. Patients' motivation is known to influence the enrollment period [30]. According to the results of the present study, regardless of the efficacy results of the clinical trials in the prior phase, study design and novelty of the investigational drugs may have increased the motivation of patients and investigators and lead to shortening of the patients' enrollment period. As previously noted, shorter patients' enrollment period would also increase the probability of success of phase III trials by allowing the study to be conducted in a less changing

external environment. It is desirable that measures to shorten the patients' enrollment period are further considered, such as reflecting patients' voice to the trial design and informed consent form to make a clinical development plan easy to understand for patients, which would motivate them to enter clinical trials.

5. Conclusion

Based on the multivariate analyses utilizing the most recent and comprehensive data available, factors associated with the success of phase III trials of anticancer agents for solid tumors were identified in the present study, which will serve as useful information in investigating the design and operation plans of future clinical trials. Among others, accelerating patients' enrollment would be important so that the initial trial hypothesis will not be affected. It is expected that, based on the findings of this study, more efforts will be made to improve the probability of success of phase III trial for solid tumors from the viewpoints of trial design as well as trial operation, including the measures to shorten patients' enrollment period.

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7. Acknowledgement

First and foremost, I would like to deeply express my sincere gratitude to Professor Mamoru Narukawa for giving me the opportunity to attend Kitasato university and providing meaningful advice and clear directions for this study from beginning to end. I would like to also thank my colleagues in the same class, members of the laboratory, and Dr. Masayuki Kaneko for providing good advice and insightful suggestion at seminars in this laboratory.

I would like to offer my special thanks to Ms. Yukiko Minami for her kind support on my student life at Kitasato university.

I would like to express my sincere gratitude to Professor Yuji Yoshiyama, Professor Nobuhiko Okada, and Associate Professor Mitsuhiro Sugawara for their reviews and helpful discussion on this study.

Finally, I want to thank my wife, who was always willing to help me, and my son, who motivated me.