Optimization of toxicity management in drug development in oncology

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Abstract

In oncology drug development, a recommended dose and toxicity management are determined at the early clinical development stage. Whereas clinical study data based on a small number of patients on early phase needs to be used for aiming at early approval, such as a strategy for rare cancers and a strategy to precede large-scale studies. However, safety profile can be difficulty determined on these strategies and safety information on early phase becomes more importance. This research was conducted to address the optimal approach to risk minimization in terms of patient safety.

Research 1 aimed to investigate the predictive factors for severe adverse events (AEs) in phase 3 trials based on phase 1 trial data. The data on phase 1 and phase 3 trials applied for their marketing approval of the newly approved anticancer drugs in Japan were used for analysis. Regression analyses were performed to investigate factors related to the predictability of the occurrence of severe AEs in phase 3 trials based on phase 1 trial data.

Thirty-two drugs (80 phase 1 trials and 40 phase 3 trials) were selected for the analyses. As a result of multivariate regression analyses, immune therapy agents ($P = 0.009$) and a pair of monotherapy in the phase 1 trials and combination therapy in the phase 3 trials ($P = 0.017$) were associated with low predictability of severe AEs in the phase 3 trials; signal inhibitor agents ($P = 0.002$) and large number of subjects in phase 1 trials ($P = 0.008$) were associated with high predictability. A significant relationship between the actual number of subjects in phase 1 trials and the predictability of severe AEs was observed when trials for immune checkpoint inhibitors were excluded ($P < 0.001$).

Research 2 aimed to investigate the effect of the addition of immune checkpoint inhibitors (ICIs) to multiple tyrosine kinase inhibitors (multi-TKIs) on the profile of treatment-related adverse events. PubMed was searched to identify published clinical studies on multi-TKI monotherapy and multi-TKI plus ICI combination therapy from July 20, 2005, to September 1, 2022. The incidence rate of common AEs caused by multi-TKI monotherapy and multi-TKI plus ICI combination therapy was obtained and compared from the viewpoints of (1) relative risk for the combination therapy versus sunitinib, (2) AE incidence rate by clinical trial, and (3) pooled incidence rate.

This systematic review identified 72 clinical studies involving 7580 patients. The

combination therapy of multi-TKI and ICI was associated with an increased risk of diarrhea, hypothyroidism, and rash compared with multi-TKI monotherapy. The addition of ICI was suggested to decrease the risk of AEs related to performance status.

Toxicity management is relatively straightforward for anti-cancer drugs of which AEs associated with the mechanism of action are known. While pathognomonic AEs for signal inhibitor agents can be identified earlier in the development process, ICIs and combination therapy could pose a huge challenge in toxicity management. Collaboration with not only oncologists but also appropriate specialists is needed. In clinical development of combination therapy with other drugs, safety assessment of the combination therapy at early phase is considered significant for understanding the toxicity profile. In case of the presence of precedent trials with the same pharmacological class of drugs, their safety data can be a useful reference. A stepwise development strategy should be considered to mitigate the risk.

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Abbreviations

AEs	Adverse events
AST	Aspartate aminotransferase increased
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase increased
BTC	Biliary tract cancer
CI	Confidence interval
CRC	Colorectal cancer
CRPC	Castration-resistant prostate cancer
CTD	Common Technical Document
DLBCL	Diffuse large B cell Lymphoma
DLT	Dose-limiting toxicity
EML4	Echinoderm microtubule-associated protein-like 4
ESCC	Esophageal squamous cell carcinoma
GC	Gastric cancer
GIST	Gastrointestinal stromal tumor
GTN	Gestational trophoblastic neoplasia
HCC	Hepatocellular carcinoma
HNSCC	Head and neck squamous cell carcinoma
ICI	Immune checkpoint inhibitor
IQR	Interquartile range
irAE	Immune-related adverse event
MCC	merkel cell carcinoma
MOA	Mechanism of action
MTC	Medullary thyroid cancer
MTD	Maximum tolerated dose
multi-TKI	Multiple tyrosine kinase inhibitor
NSCLC	Non-small cell lung cancer
N.A.	Not applicable
PD-1	Programmed death receptor-1
PD-L1	Programmed death ligand-1

RCC	Renal cell carcinoma
RR	Relative risk
SCLC	Small cell lung cancer
SE	Standard error
SGC	Salivary gland cancer
TNBC	Triple-negative breast cancer
TRAEs	Treatment-related adverse events
UC	Urothelial carcinoma
UICC	Union for international cancer control

1. Introduction

Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020 [1]. The mortality of cancers varies greatly by stage. Five-year survival rates (diagnosed in 2011-2013) in Japan were 94.0, 80.3, 57.5, and 23.0% in stage I, II, III, and IV (UICC: Union for International Cancer Control), respectively [2]. Therefore, early detection has been of great importance, and appropriate treatment has shown to contribute to survival benefit [3]. The method of treatment such as surgery, radiotherapy, and/or systemic therapy, is selected based on stage and type of cancer. Surgery is the first choice for early-stage cancer, and systemic chemotherapy is the treatment of choice for advanced/metastatic cancer. It should be noted that, while anti-cancer drugs destroy cancer cells or inhibit cancer cell growth, they also cause severe adverse events (AEs) by attacking normal tissues. Even if severe AEs are observed but the benefit outweigh the risk, the drug obtains marketing approval.

In oncology clinical development, phase 1 clinical trials are usually conducted in cancer patients considering the toxicity of anti-cancer drugs, in which recommended dose is determined and information on toxicity management is investigated [4]. However, a variety of factors are associated with the difficulty in conducting these activities. For instance, the blood levels of therapeutic and toxic area are close for many anti-cancer drugs, and the development is often conducted in combination therapy of multiple drugs. Furthermore, various development strategies are pursued depending on the characteristics of the drug and the target cancer type, such as a strategy to obtain marketing approval based on early clinical study data for rare cancers (including populations with specific driver mutation) and a strategy to jump to a large-scale study after phase 1 aiming at early approval, which would further complicate the consideration. Even under these conditions, an adequate development strategy should be constructed with sufficient consideration for patient safety based on limited data from a small number of patients at the early clinical development stage. However, few research in oncology clinical development has addressed the optimal approach to risk minimization in terms of patient safety.

The objective of this research is to explore measures for optimizing toxicity management in the development of anti-cancer drugs under the situation where

available information is limited (i.e., early phase clinical trials with limited safety data). In Research 1, to examine the importance and limitation of safety information in phase 1 trials, we investigated predictive factors for severe AEs in phase 3 trials based on safety information in phase 1. In Research 2, to examine the effect of adding an immune checkpoint inhibitor (ICI) to a multiple tyrosine kinase inhibitor (multi-TKI) on the safety profile, we conducted a systematic review based on clinical studies of multi-TKI monotherapy and combination therapy of multi-TKIs and ICIs.

2. Predictability of severe adverse events in phase 3 trials from safety information on phase 1 trials (Research 1)

2.1. Background

In oncology drug development, phase 1 trials are conducted to confirm the tolerability of the drug in cancer patients and decide a recommended dose in phase 2 trials [5]. The first cycle of treatment in a phase 1 trial is primarily intended to confirm the maximum tolerated dose (MTD) by examining the presence of the dose-limiting toxicity (DLT). The number of patients enrolled in a phase 1 trial is often small and only a few or none of the patients experience DLTs. In a retrospective analysis data of 777 patients enrolled in phase 1 trials of 54 single-agent anticancer drugs, DLTs were observed in only 11.1% of the patients [6]. This implies that the amount of safety information obtained during phase 1 trials would hardly be sufficient in planning for later clinical trials.

A variety of molecular-targeted agents for specific populations have been developed and marketed since the approval of trastuzumab as the first molecular-targeted agent for the treatment of metastatic breast cancer in 1998 [7]. These include crizotinib, ceritinib, and alectinib, in patients with EML4 (echinoderm microtubule-associated protein-like 4)-ALK (anaplastic lymphoma kinase) rearranged nonsmall-cell lung cancer [8–10], and vemurafenib in patients with BRAFV600E mutation-positive metastatic melanoma [11]. Patients in phase 1 trials for such agents were selected by using predictive biomarkers. This approach may enhance the efficacy of targeted agents and shorten their development period [12]. However, it was reported that, in 467 oncology clinical trials, MTDs were confirmed only in 64% of targeted agents, while in 99% of cytotoxic agents [13]. Low incidence of DLTs and low probability of confirming MTDs in molecular- targeted agents phase 1 trials may reduce the possibility of providing helpful information for later trials.

A phase 2 trial may be bypassed to conduct a phase 3 trial when a dramatic clinical benefit of a drug is shown in the phase 1 trials [14]. Furthermore, some drugs targeting patients with specific gene mutations were approved based on data from early clinical trials, without conducting phase 3 trials [8–11, 15]. Additionally, the efficacy and safety of novel targeted agents are often evaluated along with standard therapy or another

novel agent [16]. These present greater challenges in the interpretation of safety information on phase 1 trials despite the significance. Nevertheless, the prediction of severe adverse events (AEs) based on the information in early phase trials would be critical in oncology drug development.

Jardim et al. [17], examining the possibility of predicting toxicities in later clinical trials based on the safety information on phase 1 trials, observed significant relationship between the number of patients included in the trials and the ability to describe future clinically relevant toxicities [17]. However, the predictability of severe AEs in late, large clinical trials based on safety information from phase 1 trials and the factors affecting the predictability have not been exhaustively examined in any study.

Here, to examine the importance and limitation of safety information in phase 1 trials, we investigated the predictive factors for severe AEs in phase 3 trials based on safety information in phase 1 trials. Furthermore, severe AEs which frequently occurred in phase 3 trials, but less predictable from phase 1 trial data, were explored.

2.2. Methods

Study Selection

Anticancer drugs containing new active substances approved in Japan between 1999 and 2018 were searched using the Pharmaceuticals and Medical Devices Agency website. For the identified anticancer drugs, phase 3 trials conducted for their marketing approval were examined based on the Common Technical Document (CTD) for new drug application, and those meeting the following criteria were selected: (i) more than 100 subjects were enrolled in the trial and (ii) severe AEs (grade ≥ 3) were observed in ≥ 1% of subjects in the trial. Next, corresponding phase 1 trials conducted before the selected phase 3 trials, with those having AEs in ≥ 20% of the subjects, were selected for evaluation. This criterion was set because, in general, AEs occurring in at least 1 of 5 subjects (20%) should be carefully monitored. Phase 1 trials conducted in healthy volunteers, pediatric patients, or renal/hepatic impaired patients were excluded.

Data extraction

For each of the selected phase 3 trials, the following information was extracted from the CTD:

- mechanism of action (MOA) of the drug,
- number of corresponding phase 1 trials conducted before the phase 3 trial,
- number of subjects, type of therapy (mono/combination), tumor type of the subjects, and all the AEs observed in ≥ 20% of subjects in each of the corresponding phase 1 trials,
- number of subjects, type of therapy (mono/combination), tumor type of the subjects, and all the severe AEs (grade ≥ 3) observed in ≥ 1% of subjects in the phase 3 trial.

All the terminologies of the AEs were translated into English using MedDRA 22.0J.

Variables Used in the Investigation of the Predictability of AEs

To investigate the predictability of severe AEs in phase 3 trials from the safety information on phase 1 trials, we first classified all the AEs observed either in the phase 3 trials (grade 3 to 5, incidence ≥ 1%) or in the corresponding phase 1 trials (incidence ≥ 20%) into the following three categories.

Category A: AE observed both in phase 1 and in phase 3.

Category B: AE observed in phase 1, but not in phase 3.

Category C: AE observed in phase 3, but not in phase 1.

When multiple phase 1 trials were conducted before a phase 3 trial, all the trials that met the criteria were considered in the analysis. Based on the categories above, “disagreement rate” (dividing the number of AEs in Category C by the sum of AEs in Category A, B, and C) and “agreement rate” (dividing the number of AEs in Category A by the sum of AEs in Category A, B, and C) were calculated for each of the phase 3 trials.

Next, we defined the variables to be used in the regression analyses for the

disagreement and agreement rates. We set six variables: “MOA of the drug,” “the total number of phase 1 trials,” “the total number of subjects in phase 1 trials,” “tumor type in phase 1 trials,” “tumor type in phase 1 and phase 3 trials,” and “types of therapy in phase 1 and phase 3 trials.”

“MOA of the drug” was classified into four categories: cytotoxic agent, signal inhibitor agent, immune therapy agent and others. Signal inhibitor agent was defined as an anticancer agent that inhibits intracellular and extracellular signal transduction. Immune therapy agent was identified based on the anatomical therapeutic chemical classification and the MOA that regulates immune cells.

“The total number of phase 1 trials” was categorized into two: ≤ 2 or > 2. “The total number of subjects in phase 1 trials” was also categorized into two by referring to the median as follows: $<$ median or $\geq$ median.

“Tumor type in phase 1 trials” was divided into two categories: a specific tumor (e.g., lung cancer) and various solid/hematologic malignancies. “The tumor type in phase 1 and phase 3 trials,” was classified as “same”, if the tumor type in the phase 3 trial was the same with at least one in phase 1 trial and as “different” if otherwise.

Considering the development strategy of each drug, “types of therapy in phase 1 and phase 3 trials” were classified into four categories: mono/mono (monotherapy in both the phase 1 and phase 3 trials), combo/combo (combination therapy in both the phase 1 and phase 3 trials), mono/combo (monotherapy in phase 1 and combination therapy in the phase 3 trials), and combo/mono (combination therapy in phase 1 and monotherapy in the phase 3 trials). When multiple phase 1 trials existed and at least one trial included combination therapy, it was taken as combination therapy.

Regression Analysis

Firstly, univariate regression analysis was conducted using the disagreement rate (as a response variable) and the six variables mentioned above (as exploratory variables) to investigate factors that hamper the predictability of the occurrence of severe AEs in phase 3 trials, from the information obtained in phase 1 trials. The variables that suggested association in the univariate analysis ($P < 0.1$) were selected for the multivariate model; when a strong association (Cramér’s $V > 0.5$) was identified

between the selected explanatory variables, one of the variables was selected and included in the multivariate model. The multivariate regression analysis was performed with a statistically significant association defined as $P < 0.05$.

Similarly, we investigated the factors related to the predictability of the occurrence of severe AEs in phase 3 trials based on the safety information obtained in the phase 1 trials. Univariate and multivariate regression analyses were conducted using the agreement rate for each phase 3 trial as a response variable. Additionally, a univariate regression analysis was conducted to investigate an association between the actual number of subjects in phase 1 trials and the agreement rate for each phase 3 trial.

Investigation of Frequent and Unpredictable AEs

For each AE terminology identified either in phase 1 or in the phase 3 trials, the numbers in Categories A, B, and C were counted. The “indicator of unpredictable AE” was calculated by dividing Category C by the sum of Categories A, B, and C. To investigate the frequency of occurrence for severe AEs in phase 3 trials that were difficult to predict based on safety data from phase 1 trials, a figure with “indicator of unpredictable AE” on the vertical axis and “ratio of phase 3 trials in which the AE was observed” on the horizontal axis was created.

All the analyses were performed using StatsDirect (Stats-Direct LTD., Cheshire, UK).

2.3. Results

Search Results and Trial Characteristics

Ninety-six anticancer drugs with new active substances approved between 1999 and 2018 in Japan were identified. Among them, 32 drugs with 40 phase 3 trials and corresponding 80 phase 1 trials met the criteria and were selected for the analysis (Fig. 1).

There were 4240 subjects in the 80 phase 1 trials and 14132 subjects in the 40 phase 3 trials. The accumulated number of AE terms from all the trials was 367. The characteristics of the 32 drugs and 80 phase 3 trials are shown in Table 1. Signal

inhibitor agents and immune therapy agents were 15 (46.9%) and 10 (31.3%), respectively. Approximately 30% of the drugs included trials evaluating combination therapy in phase 1 or phase 3 trials. The same tumor type was evaluated in phase 1 and 3 trials for 68.8% of the drugs. Other characteristics are described in Supplemental Table 8.

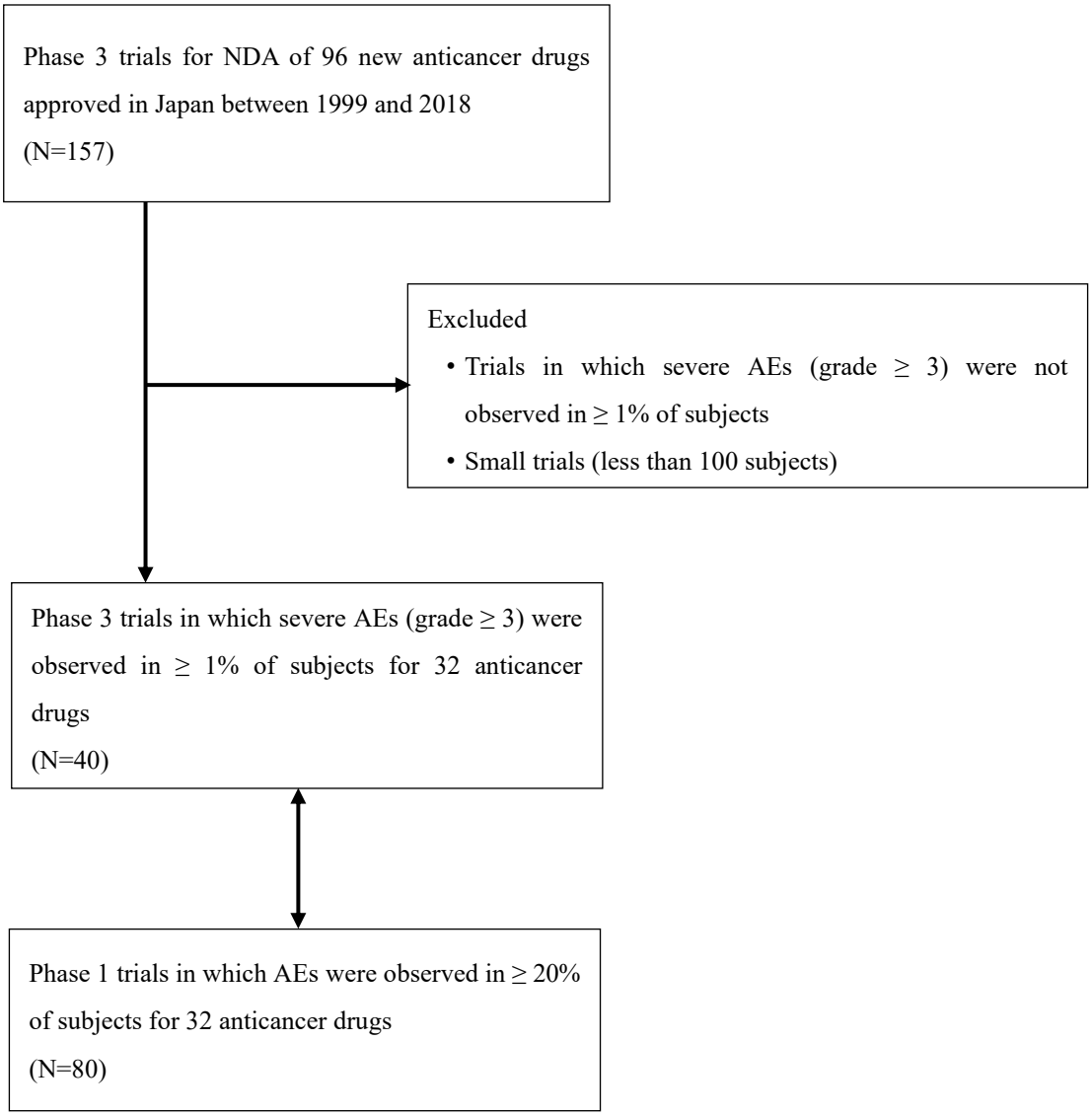


Figure 1. Study selection

Table 1. Characteristics of drugs and Phase 3 trials

Drugs (n=32)	**N (%)**
Mechanism of action	
Cytotoxic agents	4 (12.5)
Signal inhibitor agents	15 (46.9)
Immune therapy agents	10 (31.3)
Other	3 (9.4)
Median of total number of phase 1 trials (IQR)	2 (2-3)
Median of total number of subjects in phase 1 trials (IQR)	92 (43-155)
Types of therapy in phase 1 trials	
Include combination therapy	10 (31.3)
Monotherapy only	22 (68.8)
Tumor type in phase 1 trials	
Specific tumor	19 (59.4)
Solid/Hematologic malignancies	13 (40.6)
Phase 3 trials (n=40)	**N (%)**
Types of therapy in phase 3 trial	
Combination therapy	13 (32.5)
Monotherapy only	27 (67.5)
Tumor type in phase 1 and phase 3 trials	
Same	27 (67.5)
Different	13 (32.5)

Abbreviations: IQR, Interquartile range.

Investigation of the Predictability of AEs by Regression Analysis

The univariate and multivariate regression analyses were conducted to investigate the factors that hamper the predictability of severe AEs in phase 3 trials from the information obtained in phase 1 trials. This was performed using the disagreement rate for each phase 3 trial as a response variable (Supplemental Table 9). The median disagreement rate was 35.3% for the 40 phase 3 trials. From the univariate analysis, two factors, "MOA of the drug" and "types of therapy in phase 1 and phase 3 trials," were selected as candidates for the multivariate analysis ($P < 0.1$) (Table 2). There was no strong association between the two variables (Cramer's $V = 0.198$), and they were included in the multivariate analysis. Consequently, both variables indicated associated with the disagreement rate. Regarding "types of therapy in phase 1 and phase 3 trials," mono/combo significantly increased the disagreement rate compared to mono/mono and combo/combo ($P = 0.017$). For "MOA of the drug," immune therapy agents were associated with a significant increase in the disagreement rate relative to signal inhibitor agents ($P = 0.009$) (Table 2).

Another regression analysis using the agreement rate for each phase 3 trial as a response variable was conducted to identify the factors related to the predictability of the occurrence of severe AEs in phase 3 trials based on the safety information obtained in the phase 1 trials. Results for the agreement rate for each phase 3 trial are shown in Supplemental Table 9. The median agreement rate was 19.6% for the 40 phase 3 trials. The univariate analysis showed three factors, "MOA of the drug", "the total number of subjects in phase 1 trials," and "the total number of phase 1 trials," that were potentially associated with the agreement rate ($P < 0.1$) (Table 3). A strong association was identified between "the total number of subjects in phase 1 trials" and "the total number of phase 1 trials" (Cramer's $V = 0.558$), and "MOA of the drug" and "the total number of subjects in phase 1 trials" were selected as exploratory variables for the multivariate analysis. As a result, both variables showed association with the agreement rate. Regarding the MOA, "signal inhibitor agents" presented a significant increase in the agreement rate compared to "immune therapy agents" ($P = 0.002$) (Table 3).

Increasing the number of patients enrolled in early clinical trials is often considered to improve the predictability of severe AEs in later trials because more safety

information has been accumulated. The result of the multivariate analysis showed that large number of subjects in phase 1 trials (≥ 92) regarding “the total number of subjects in phase 1 trials” was associated with the agreement rate (P = 0.008) (Table 3). Thus, we investigated the correlation between the actual number of subjects in phase 1 trials and the agreement rate. However, this was not significant (correlation coefficient = − 0.075; Supplemental Fig. 5). Due to the low median agreement rate (13.3%) for immune checkpoint inhibitors (ICIs) compared to other drugs (23.4%), we investigated the correlation for all the phase 3 trials except for 5 trials with ICIs. As a result, the number of subjects in phase 1 trials significantly correlated with the agreement rate (correlation coefficient = 0.585; P < 0.001, Fig. 2).

Table 2. Results of univariate and multivariate analysis for the relationship between the disagreement rate and several variables

Variable	**Univariate Analysis**			**Multivariate Analysis**		
	Coefficient	SE	P value	Coefficient	SE	P value
MOA of the drug						
Signal inhibitor agents	Reference			Reference		
Cytotoxic agents	5.64	9.18	0.543	1.58	8.82	0.859
Immune therapy agents	18.62	5.96	0.004	16.38	5.88	0.009
Other	14.32	8.40	0.097	14.46	8.11	0.084
Total number of phase 1						
< 2	Reference					
> 2	-6.61	5.96	0.274			
Total number of subjects in						
< 92	Reference					
> 92	-5.99	5.72	0.302			
Tumor type in phase 1 trials						
Specific tumor	Reference					
Solid/ hematologic	-1.15	6.30	0.856			
Tumor type in phase 1 and						
Same	Reference					
Different	2.26	6.46	0.728			
Types of therapy in phase 1						
Mono/mono or Combo/combo	Reference			Reference		
Mono/combo	21.82	8.21	0.012	19.50	7.79	0.017
Combo/mono	1.76	7.60	0.818	4.49	7.45	0.551

Abbreviations: SE, standard error; MOA, mechanism of action; Mono/mono, a pair of monotherapy in both the phase 1 and phase 3 trials; Combo/combo, a pair of combination therapy in both the phase 1 and phase 3 trials; Mono/combo, a pair of monotherapy in phase 1 and combination therapy in the phase 3 trials; Combo/mono, a pair of combination therapy in phase 1 and monotherapy in the phase 3 trials.

Table 3. Results of univariate and multivariate analysis for the relationship between the agreement rate and several variables

Variable	Univariate Analysis			Multivariable Analysis		
	Coefficient	SE	P value	Coefficient	SE	P value
MOA of the drug						
Signal inhibitor agents	Reference			Reference		
Cytotoxic agents	-1.07	4.61	0.819	2.62	4.42	0.557
Immune therapy agents	-8.20	3.00	0.010	-9.55	2.79	0.002
Other	3.15	4.22	0.460	-1.00	4.14	0.811
Total number of phase 1						
< 2	Reference					
> 2	5.63	2.91	0.060			
Total number of subjects in						
< 92	Reference					
> 92	5.78	2.77	0.044	7.84	2.79	0.008
Tumor type in phase 1 trials						
Specific tumor	Reference					
Solid/ hematologic	-3.43	3.12	0.280			
Tumor type in phase 1 and						
Same	Reference					
Different	-0.88	3.25	0.789			
Types of therapy in phase 1						
Mono/mono or Combo/combo	Reference					
Mono/combo	-2.86	4.42	0.522			
Combo/mono	3.83	4.09	0.356			

Abbreviations: SE, standard error; MOA, mechanism of action; Mono/mono, a pair of monotherapy in both the phase 1 and phase 3 trials; Combo/combo, a pair of combination therapy in both the phase 1 and phase 3 trials; Mono/combo, a pair of monotherapy in phase 1 and combination therapy in the phase 3 trials; Combo/mono, a pair of combination therapy in phase 1 and monotherapy in the phase 3 trials.

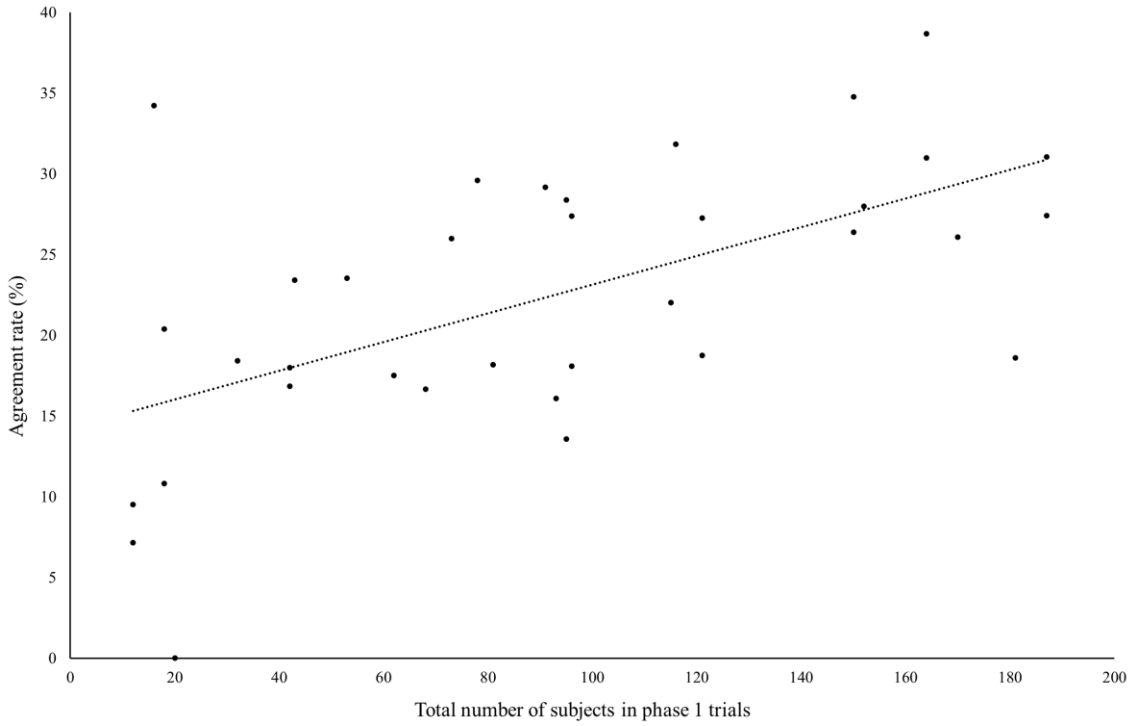


Figure 2. Correlation between agreement rate for each phase 3 trial and total number of subjects in phase 1 trials except for clinical trials with immune checkpoint inhibitors.

Investigation of Frequent and Unpredictable AEs

Figure 3 shows the relationship between “ratio of phase 3 trials in which AE was observed” and “indicator of unpredictable AEs.” Asthenia (76.0%), pneumonia (75.9%), hyponatraemia (66.7%), hypertension (55.6%), and hypokalaemia (52.0%) were AEs which indicated high values of “indicator of unpredictable AEs” and frequently occurred in phase 3 trials. In contrast, fatigue, diarrhea, back pain, and nausea represented low values of “indicator of unpredictable AEs” and frequently occurred in phase 3 trials, which were commonly reported in both phase 1 and phase 3 trials.

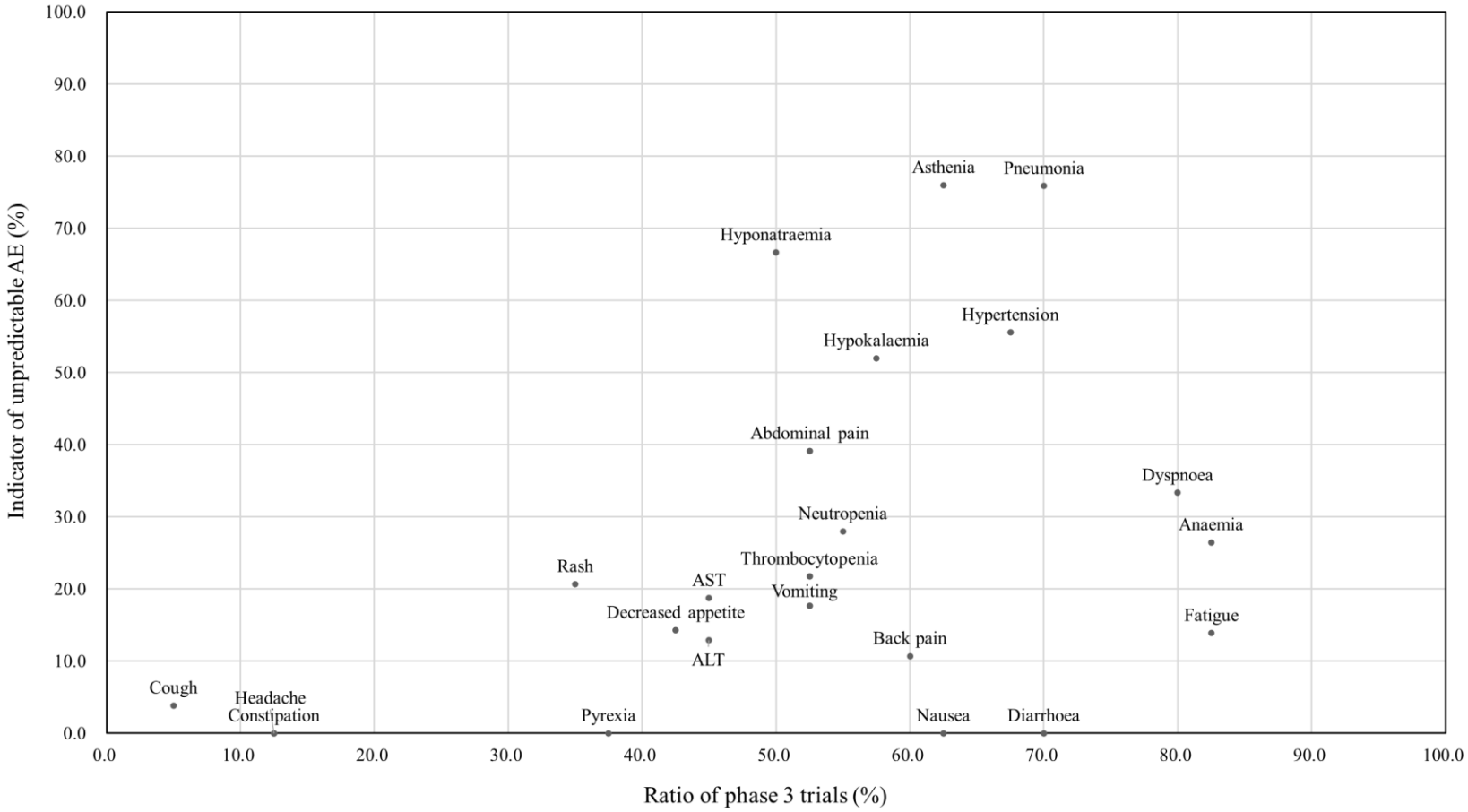


Figure 3. Scatter plot illustrating the relationship between the ratio of phase 3 trials in which adverse event was observed and the indicator of unpredictable adverse event.

Abbreviations: AE, Adverse Event; AST, Aspartate aminotransferase increased; ALT, Alanine aminotransferase increased.

AEs shown in the Figure are limited to those which occurred more than half of either phase 1 (80 studies) or phase 3 (40 studies).

2.4. Discussion

The possibility of predicting severe AEs in phase 3 trials based on safety data from phase 1 trials was investigated in this study. Immune therapy agents as MOA of the drug and “mono/combo” (monotherapy in the phase 1 and combination therapy in the phase 3 trials) as types of therapy in phase 1 and phase 3 trials were associated with a significant increase in the disagreement rate. This means that both are possible factors that would lead to difficulties in predicting severe AEs in phase 3 trials based on the phase 1 trial data. Conversely, signal inhibitor agents and large number of subjects in phase 1 trials (≥ 92) were associated with a significant increase in the agreement rate, indicating that both are possible factors that would contribute to enhancing the predictability of severe AEs in phase 3 trials. These results suggest that phase 1 trials with combination therapy should be conducted in advance if phase 3 trials with combination therapy are planned. Since combination therapies have increased the incidence of severe AEs [18], one key to successful phase 3 trials is to collect safety information about combination therapies in early trials and effectively manage severe AEs in the phase 3 trial. Furthermore, it was suggested that clinical trials with immune therapy agents should be planned and conducted cautiously compared to trials with signal inhibitor agents, due to lesser ability to predict severe AEs in phase 3 trials. If other drugs with the same MOA have undergone large-scale studies, their safety information may serve as a reference. For example, ICIs showed predominant association with pruritus, rash, diarrhea, colitis, hypothyroidism, hyperthyroidism, and pneumonitis [19]. Therefore, it would be advisable to pay attention to such information. At the same time, toxicity from combination therapy could be changed based on dosage and drugs used in the combination [20, 21]. Besides consulting an oncologist, it is also important and appropriate to consult a toxicologist and a specialist on the management of toxicities.

There was a significant correlation between the agreement rate and the actual number of subjects in phase 1 trials when trials evaluating ICIs were excluded. In a case where a small number of patients were evaluated in a phase 1 trial, an expansion cohort was set to increase the number of patients for safety and efficacy assessment in the phase 1 trial [22]. Setting up an expansion cohort could be one method of accumulating

enough safety information when a large phase 3 trial without phase 2 trials data is conducted or approval of an anticancer drug based on data from phase 1 trials is intended. A new drug application for a rare cancer is usually based on study data of early clinical trials which have inadequate safety information. The present study revealed that tumor type in phase 1 trials did not affect the predictivity of severe AEs in phase 3 trials, and therefore, conducting early phase trials that target various carcinomas to increase the amount of safety information is an alternative.

ICIs had a lower agreement rate compared with other drugs. Even if more patients were enrolled in phase 1 trials for ICIs, the predictability of severe AEs might not be improved. The increase in immune activation caused by ICIs in normal tissues may be responsible for various types of significant immune-related AEs (irAEs) throughout the body [23]. According to Costa and colleagues, the most common irAEs observed in phase 1 and late-phase trials for ICIs were generally similar and sample size of phase 1 trials was correlated with the concordance of common AE frequencies observed in phase 1 and late-phase trials. This result was obtained from pooled data of 10 phase 1 and 15 late-phase trials for three types of ICIs [24]. In the clinical development of a new immune checkpoint inhibitor agent, a development program for its late-phase trials needs to be prepared based on preceding phase 1 trial data for the agent. Thus, because the prediction of potential AEs expected in late-phase trials is especially difficult for ICIs, it would be important to explore appropriate design and scale of phase 1 trials including setting up expansion cohorts, and to adopt a more cautious approach to monitoring the safety of subjects in the late-phase trials. Presumably, the importance of predicting severe AEs based on safety information on phase 1 trials would be significant as development of ICIs becomes more active.

Asthenia, pneumonia, hyponatraemia, hypertension, and hypokalaemia were identified as remarkable severe AEs that would be difficult to predict from safety information in phase 1 trials. These severe AEs are absent in early trials probably due to the small number of patients but are unexpectedly observed in large clinical trials. Although these severe AEs do not tend to occur in phase 1 trials, they should be routinely monitored for early detection and treated without delay. In contrast, fatigue, diarrhea, nausea, and back pain could occur in any stage of oncology drug development,

thus, the occurrence of these AEs should be monitored from early phase through late-phase clinical trials.

There are several limitations in this study. Firstly, various dosage and dosing schedules were used in the phase 1 trials, but these data were evaluated without distinction of the different dosage and dosing schedules. Secondly, types of concurrent anticancer drugs for combination therapy were not specified in the present study because the target tumor type for approval was not identified and various types of concurrent anticancer drugs were tested at the time of phase 1 trials in many cases. Thirdly, we collected data of phase 1 and phase 3 trials in which AEs were observed in ≥ 20% and ≥ 1% of subjects, respectively, for the analyses. There is no established threshold for the incidence of AEs observed in early clinical trials to which due attention should be paid in the later stage, and we set 20% as a threshold value for phase 1 trials. And although we set a threshold of 1% for phase 3 trials, it is also important to monitor uncommon severe AEs in phase 3 trials. Therefore, the results of the present study should be interpreted cautiously. Finally, safety information was collected from the CTD of drugs that were approved by the authorities, and the data from unsuccessful clinical trials were not included in the study.

In conclusion, we investigated the possibility of predicting severe AEs in phase 3 trials based on safety data from phase 1 trials and identified the factors that were related to the predictability. Additionally, remarkable severe AEs that should be anticipated in late clinical trials although not specified as safety risks in phase 1 trials were identified. This should be effectively utilized for the strategic design of early-stage oncology drug development.

3. Systematic review of adverse events for combination therapy of multiple tyrosine kinase inhibitor and immune checkpoint inhibitor (Research 2)

3.1. Background

In recent years, new anti-cancer drugs, molecular-targeted agents, and antibody drugs have been developed as replacements of conventional cytotoxic compounds. Since the approval of trastuzumab as the first molecular-targeted agent for the treatment of metastatic breast cancer in the US in 1998 [7], a variety of molecular-targeted agents for specific populations have been developed. Multiple tyrosine kinase inhibitors (multi-TKIs) targeting multiple molecules have been shown to be effective in several cancers, and several multi-TKIs, such as sorafenib, sunitinib, axitinib, pazopanib, and cabozantinib have been used in clinical practice [25, 26]. It has also been reported that multi-TKIs cause pathognomonic toxicities, such as diarrhea, fatigue, nausea, rash, anorexia, vomiting, hand-foot syndrome, hypertension, and proteinuria, which are typical toxicities for multi-TKIs [27, 28].

Recently, various immunotherapies have been actively developed. In 2011, ipilimumab, the first immune checkpoint inhibitor (ICI), was approved for treating melanoma in the US. [29]. Among the various types of ICIs, programmed death receptor-1 (PD-1) / programmed death ligand-1 (PD-L1) inhibitors have been actively developed and indications for various types of cancer have been obtained. PD-1 is overexpressed in dendritic cells and T cells in the tumor environment and binds to PD-L1/PD-L2, which is expressed in cancer cells, to suppress the activity of immune cells, such as T cells and inhibit immune responses [30-32]. Blockade of the PD-1/PD-L1 pathway can activate immune responses and enhance anti-tumor effects. Several clinical studies have been conducted on PD-1/PD-L1 inhibitors, and sufficient safety information has been accumulated to understand their safety profile. Safety analyses have been comprehensively performed, and it was shown that these drugs cause immune-related toxicity in various parts of the body [33].

Several clinical studies have been conducted on the use of PD-1/PD-L1 inhibitors in combination with other medications, including multi-TKIs for treating various cancers. Non-clinical data suggest that multi-TKIs produce higher T-cell activation and macrophage polarization, indicating immunomodulatory effects that enhance synergistic

anti-tumor efficacy [34]. In recent years, an increasing number of studies using multi-TKIs plus ICIs have been conducted, and several ICIs (avelumab, pembrolizumab, and nivolumab) in combination with multi-TKIs (axitinib, lenvatinib, and cabozantinib) have been approved for the treatment of renal cell cancer [35]. It is assumed that the combination therapy of multi-TKIs and ICIs will be developed for other types of cancer. Therefore, in addition to efficacy, understanding the safety profile of this combination therapy is crucial for toxicity management. Few large-scale studies have investigated multi-TKI plus ICI combination therapy, which makes a comprehensive safety analysis difficult. Moreover, safety assessment of multi-TKI plus ICI combination therapies based on large-scale studies is considered insufficient because the types of multi-TKIs used in the experimental arm and the control arm are usually different.

Therefore, to examine the effect of adding ICI to multi-TKI on the safety profile, we conducted a systematic review based on the clinical studies of multi-TKI monotherapy and combination therapy of multi-TKIs and ICIs.

3.2. Methods

Study selection strategy

A systematic literature search was conducted to identify published clinical studies on multi-TKI monotherapy and those on multi-TKI plus ICI combination therapy that reported treatment-related adverse events (TRAEs) (incidence ≥10%). First, to identify ICIs to be examined in the present study, the search was conducted in PubMed using the terms PD-1, PD-L1, and inhibitor, and then the list was narrowed down using clinical trials. Second, to identify multi-TKIs that are used in combination with ICIs, the search was conducted using the generic names of the ICIs identified above and the term tyrosine kinase and the list was narrowed down using clinical trials. Finally, we searched for clinical studies on multi-TKI monotherapy and combination therapy of multi-TKI and ICI using the generic names of the multi-TKIs identified above and narrowed down the list using clinical trials. The search was conducted for clinical studies reported from July 20, 2005, to September 1, 2022.

In this study, the applicable clinical studies were included in the analysis regardless

of whether they were single-arm or randomized clinical studies. Clinical studies in healthy volunteers, pediatric patients, and patients with hepatic disorders were excluded to minimize the impact of differences in the study populations.

Data extraction

For each of the selected clinical studies, the following information was extracted and tabulated: generic name(s) of the multi-TKIs and ICIs, number of subjects, and study phase. Phase 1/2 was regarded as phase 2.

The following common adverse events (AEs) were selected for this study with reference to the package insert of multi-TKIs: anorexia, constipation, weight loss, diarrhea, fatigue, hand-foot syndrome (including palmar-plantar erythrodysesthesia syndrome), hypertension, hypothyroidism, nausea, proteinuria, rash, and vomiting. For each AE, the number of events was extracted from the clinical studies on multi-TKI monotherapy and multi-TKI plus ICI combination therapy. Incidence rates were calculated by dividing the number of events by the number of subjects in each study.

Statistical analysis

Relative risk for combination therapy with multiple tyrosine kinase inhibitors and immune checkpoint inhibitors (vs. sunitinib)

Several randomized phase 3 trials on multi-TKI plus ICI combination therapy and on sunitinib as a comparator were identified. For each of the selected AEs, the relative risk (RR) for the combination therapy of multi-TKIs and ICIs compared with sunitinib was calculated. Then, the pooled RR and 95% confidence interval (CI) were calculated using a random-effects model.

Comparison of adverse events between multiple tyrosine kinase inhibitor monotherapy and combination therapy of multiple tyrosine kinase inhibitors and immune checkpoint inhibitors (analysis by clinical trial)

For each of the selected AEs, the number of studies with ≥10% incidence and those with <10% incidence were counted separately for multi-TKI monotherapy and multi-TKI plus ICI combination therapy. Fisher's exact test was used to examine

whether there was an imbalance in the number of studies between multi-TKI monotherapy and multi-TKI plus ICI combination therapy.

Pooled incidence rate of adverse events for multiple tyrosine kinase inhibitor monotherapy and combination therapy of multiple tyrosine kinase inhibitors and immune checkpoint inhibitors

The pooled incidence rate and its 95% confidence interval for the selected AEs were calculated separately for multi-TKI monotherapy and multi-TKI plus ICI combination therapy using a random-effects model.

All analyses were performed using StatsDirect (Stats-Direct Ltd., Cheshire, UK). A statistically significant association was defined as $P<0.05$.

3.3. Results

Search results and trial characteristics

Our literature search and review of reference lists identified 549 relevant publications, from which 72 eligible studies involving 7580 patients for the analyses were selected (Supplemental Table 10). Five multi-TKIs that have been used in clinical studies in combination with ICIs were identified. Forty-seven studies were conducted on multi-TKI monotherapy, 24 studies on multi-TKI plus ICI combination therapy, and one study evaluated multi-TKI monotherapy and multi-TKI plus ICI combination therapy. The identified multi-TKIs included apatinib (n=7), axitinib (n=13), cabozantinib (n=8), lenvatinib (n=6), and regorafenib (n=14), with a total of 3882 patients receiving multi-TKIs. PD-1 and PD-L1 inhibitors used included atezolizumab (n=2), avelumab (n=3), camrelizumab (n=8), durvalumab (n=1), nivolumab (n=3), and pembrolizumab (n=8), with a total of 3698 patients receiving ICIs. Phase 2 trial was most common for both multi-TKI monotherapy (n=35) and multi-TKI plus ICI combination therapy (n=13) (Table 4).

Table 4. Trial Characteristics

	multi-TKI *monotherapy* (n=48)	**multi-TKI + ICI *combination* (n=25)**
	N (%)	**N (%)**
Total number of subjects	3,882	3,698
Phase		
1	5 (10.4)	6 (24.0)
2	35 (72.9)	13 (52.0)
3	8 (16.7)	6 (24.0)
Type of multi-TKI		
Apatinib	7 (14.6)	8 (32.0)
Axitinib	13 (27.1)	5 (20.0)
Cabozantinib	8 (16.7)	4 (16.0)
Lenvatinib	6 (12.5)	6 (24.0)
Regorafenib	14 (29.2)	2 (8.0)
Type of ICI		
Atezolizumab		2 (8.0)
Avelumab		3 (12.0)
Camrelizumab		8 (32.0)
Durvalumab		1 (4.0)
Nivolumab		3 (12.0)
Pembrolizumab		8 (32.0)
Abbreviations: ICI, immune checkpoint inhibitor; multi-TKI, multiple tyrosine kinase inhibitor		

Relative risk for the combination therapy of multiple tyrosine kinase inhibitors and immune checkpoint inhibitors (vs. sunitinib)

Four randomized controlled phase 3 trials involving 3059 patients (1524 receiving sunitinib) were included in the calculation of RR comparing TRAEs between multi-TKI plus ICI combination therapy and sunitinib (Table 5). Constipation, weight loss, and proteinuria were not included in the analysis because of insufficient number of events.

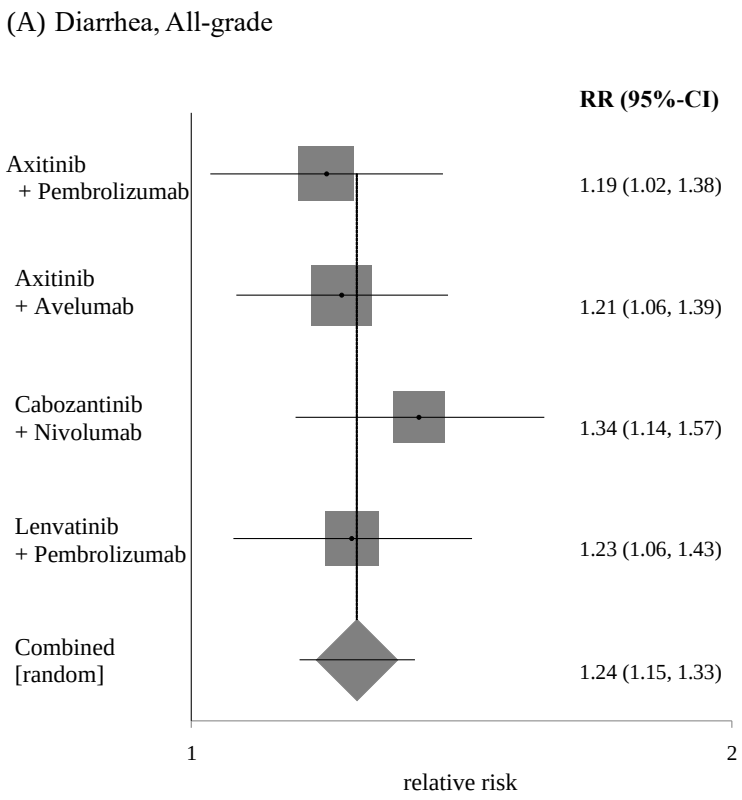
TRAEs with a statistically significant increase in RR for the multi-TKI plus ICI combination therapy compared with sunitinib were diarrhea (RR: 1.24, 95%CI: 1.15–1.33, P<0.001), hypothyroidism (RR: 1.44, 95%CI: 1.11–1.87, P=0.0064), and rash (RR: 1.71, 95%CI: 1.18–2.47, P=0.0045) (Fig 4). TRAEs with a statistically significant decrease in RR for multi-TKI plus ICI combination therapy compared with sunitinib were hand-foot syndrome (RR: 0.85, 95%CI: 0.72–1.00, P=0.0435) and nausea (RR: 0.82, 95%CI: 0.73–0.93, P=0.0016) (Fig 4). Anorexia, fatigue, hypertension and vomiting were not significantly different between the multi-TKI plus ICI combination therapy and sunitinib (Supplemental Fig 6).

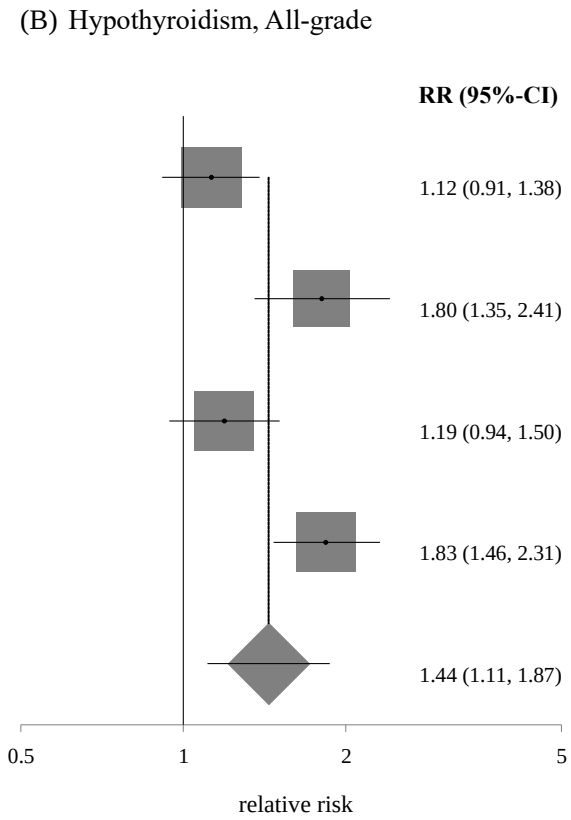
Table 5. Pooled relative risk of adverse events for immune checkpoint inhibitor plus multiple tyrosine kinase inhibitor compared with sunitinib monotherapy

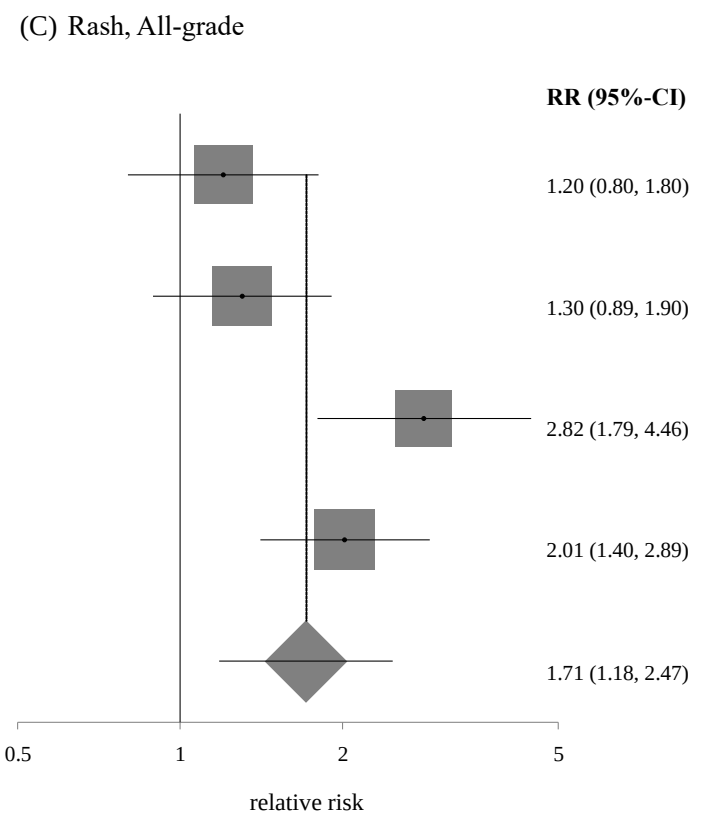
Adverse event	**Relative Risk（95% CI）**	**P value**
Anorexia	1.03 (0.77-1.39)	0.8356
Diarrhea	1.24 (1.15-1.33)	< 0.0001
Fatigue	0.95 (0.86-1.05)	0.3425
Hand-foot syndrome	0.85 (0.72-1.00)	0.0435
Hypertension	1.15 (0.91-1.45)	0.2303
Hypothyroidism	1.44 (1.11-1.87)	0.0064
Nausea	0.82 (0.73-0.93)	0.0016
Rash	1.71 (1.18-2.47)	0.0045
Vomiting	0.75 (0.54-1.04)	0.0851

*constipation, weight loss and proteinuria were not included in the analysis due to insufficient number of events.

Abbreviations: CI, confidence interval


(A) Diarrhea, All-grade
RR (95%-CI)
Axitinib + Pembrolizumab
1.19 (1.02, 1.38)
Axitinib + Avelumab
1.21 (1.06, 1.39)
Cabozantinib + Nivolumab
1.34 (1.14, 1.57)
Lenvatinib + Pembrolizumab
1.23 (1.06, 1.43)
Combined [random]
1.24 (1.15, 1.33)
1
2
relative risk


(B) Hypothyroidism, All-grade
RR (95%-CI)
1.12 (0.91, 1.38)
1.80 (1.35, 2.41)
1.19 (0.94, 1.50)
1.83 (1.46, 2.31)
1.44 (1.11, 1.87)
0.5
1
2
5
relative risk


(C) Rash, All-grade
RR (95%-CI)
1.20 (0.80, 1.80)
1.30 (0.89, 1.90)
2.82 (1.79, 4.46)
2.01 (1.40, 2.89)
1.71 (1.18, 2.47)
0.5
1
2
5
relative risk

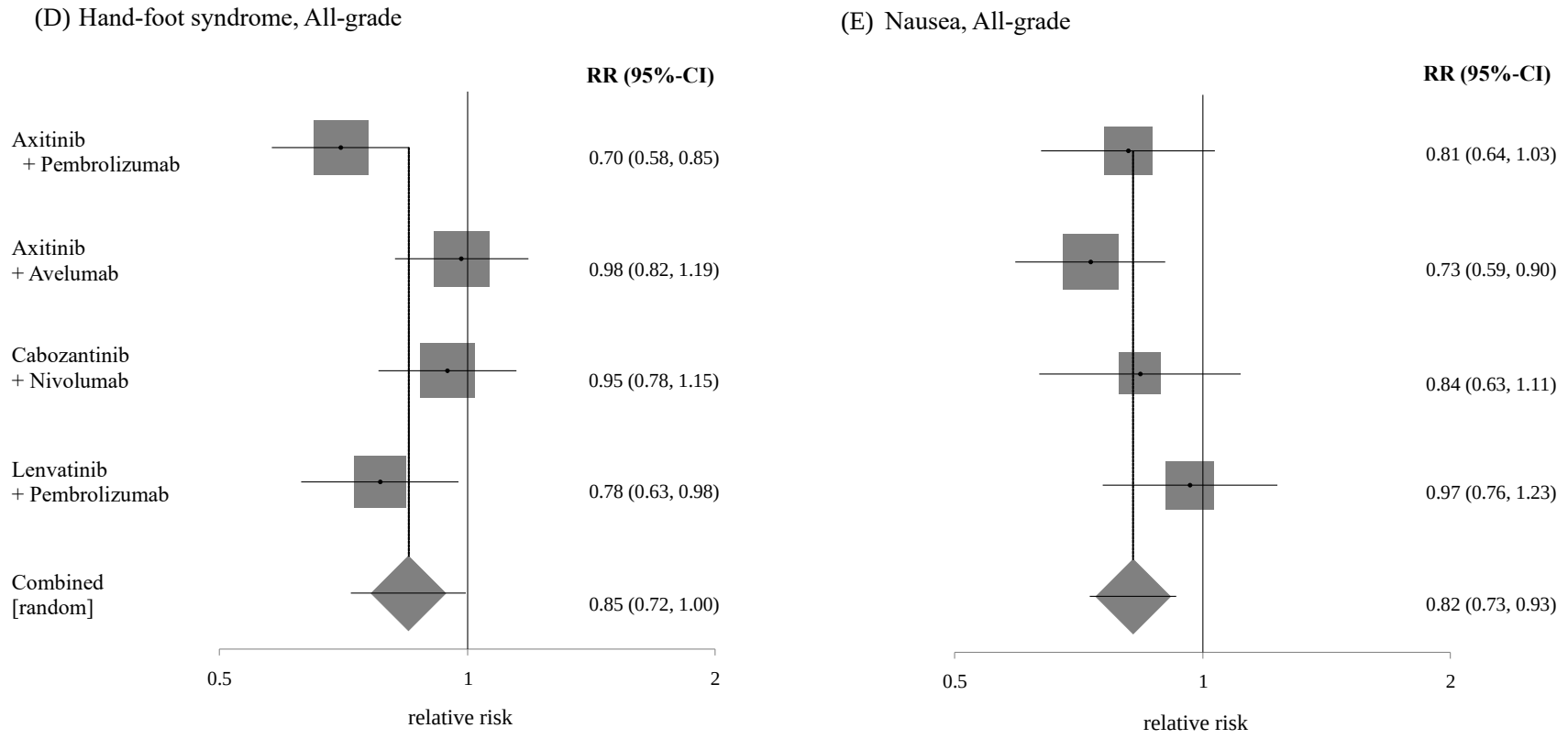


Figure 4. Forest plot of relative risk of adverse events (all grade) for (A) diarrhea, (B) hypothyroidism, (C) rash, (D) hand-foot syndrome and (E) nausea for immune checkpoint inhibitors plus multiple tyrosine kinase inhibitor compared with that of sunitinib.

Abbreviations: RR, relative risk

Comparison of adverse events between multiple tyrosine kinase inhibitor monotherapy and combination therapy of multiple tyrosine kinase inhibitors and immune checkpoint inhibitors (analysis by clinical trial)

TRAEs were compared between multi-TKI monotherapy and multi-TKI plus ICI combination therapy, focusing on whether the events occurred in more than 10% or less than 10% of the studies. The number of studies classified by the occurrence of AEs (≥10% or <10%) and P values are shown in Table 6.

In multi-TKI monotherapy, all-grade TRAEs occurred in 2267 of 2407 patients (94.2%) in 24 studies, and grade 3 or higher TRAEs occurred in 1278 of 2200 patients (58.1%) in 19 studies. In the multi-TKI plus ICI combination therapy, all-grade TRAEs occurred in 3464 of 3604 patients (96.1%) in 23 studies, and grade 3 or higher TRAEs occurred in 2274 of 3585 patients (63.4%) in 22 studies. Of the AEs with a statistically significant difference in incidence between multi-TKI monotherapy and multi-TKI plus ICI combination therapy, hypothyroidism (P=0.0001) and rash (P=0.0013) were significantly higher in the combination therapy group, and constipation (P=0.0081) was higher in the monotherapy group. There were no significant differences in the incidence of anorexia, weight loss, diarrhea, fatigue, hand-foot syndrome, hypertension, nausea, proteinuria, or vomiting.

Table 6. Number of study arms classified by frequency of adverse events for the arms of multiple tyrosine kinase inhibitor monotherapy and immune checkpoint inhibitor plus multiple tyrosine kinase inhibitor combination

		multi-TKI ***monotherapy***	**multi-TKI + ICI** ***combination***	
Adverse Event				**P value**
Anorexia	≥10%	37	21	0.5568
	<10%	11	4	
Constipation	≥10%	21	3	0.0081
	<10%	27	22	
Weight loss	≥10%	24	11	0.8054
	<10%	24	14	
Diarrhea	≥10%	44	24	0.6545
	<10%	4	1	
Fatigue	≥10%	43	21	0.4817
	<10%	5	4	
Hand-foot syndrome	≥10%	42	23	0.707
	<10%	6	2	
Hypertension	≥10%	46	25	0.5434
	<10%	2	0	
Hypothyroidism	≥10%	20	22	0.0001
	<10%	28	3	
Nausea	≥10%	36	16	0.4154
	<10%	12	9	
Proteinuria	≥10%	24	17	0.2138
	<10%	24	8	
Rash	≥10%	17	19	0.0013
	<10%	31	6	
Vomiting	≥10%	26	13	>0.9999
	<10%	22	12	

Abbreviations: ICI, immune checkpoint inhibitor; multi-TKI, multiple tyrosine kinase inhibitor

Pooled incidence rate of adverse events for multiple tyrosine kinase inhibitor monotherapy and combination therapy of multiple tyrosine kinase inhibitors and immune checkpoint inhibitors

The pooled incidence rates of each TRAE for multi-TKI monotherapy and multi-TKI plus ICI combination therapy are shown in Table 7. The most common TRAEs were hypertension (47.6% [1652/3828 patients], 46/48 studies), fatigue (47.5% [1518/3732 patients], 43/48 studies), and hand-foot syndrome (46.7% [1567/3536 patients], 42/48 studies) in the multi-TKI monotherapy group and hypertension (46.6% [1645/3698 patients], 25/25 studies), fatigue (40.9% [1141/3292 patients], 21/24 studies), and diarrhea (40.6% [1682/3646 patients] 24/25 studies) in the multi-TKI plus ICI combination therapy group. AEs with ≥5% higher incidence in monotherapy than in combination therapy were anorexia, fatigue, and hand-foot syndrome. No significant differences were found in the other AEs.

Table 7. Pooled incidence rates of adverse events for multiple tyrosine kinase inhibitor monotherapy and immune checkpoint inhibitor plus multiple tyrosine kinase inhibitor

	multi-TKI *monotherapy*		**multi-TKI + ICI *combination***	
Adverse Event	**Pooled proportion**	**95% CI**	**Pooled proportion**	**95% CI**
Anorexia	34.1	30.1-38.2	26.9	23.3-30.8
Constipation	15.6	13.8-17.5	13.2	9.3-17.7
Weight loss	24.5	19.8-29.6	19.7	16.3-23.4
Diarrhea	37.6	32.8-42.5	40.6	35.4-45.9
Fatigue	47.5	41.8-53.2	40.9	35.1-46.9
Hand-foot syndrome	46.7	41.6-53.2	34.0	29.3-38.9
Hypertension	47.6	41.5-53.8	46.6	39.4-53.9
Hypothyroidism	32.2	25.4-39.4	29.0	23.7-34.6
Nausea	27.2	22.9-31.7	26.5	21.7-31.7
Proteinuria	38.1	29.8-46.7	35.2	27.5-43.3
Rash	18.2	15.1-21.5	21.4	17.4-25.7
Vomiting	20.2	17.4-23.2	17.7	14.7-20.9

Abbreviations: ICI, immune checkpoint inhibitor; multi-TKI, multiple tyrosine kinase inhibitor; CI, confidence interval

3.4. Discussion

Combination therapy with multi-TKIs and ICIs has already been shown to be highly effective for several types of cancers, and it is expected that various combinations of multi-TKIs and ICIs will be actively examined in the future. However, the number of large-scale studies on multi-TKI and ICI combination therapy is limited, and the safety profile has not been fully elucidated. Few clinical studies have used the same multi-TKIs as a background therapy in combination with ICI, which could be one of the factors for not having clarified the impact of adding ICIs to multi-TKIs on safety. Therefore, the present study investigated the effect of adding ICIs to multi-TKIs on the safety profile from various perspectives, especially focusing on the pathognomonic toxicities derived from multi-TKIs.

In phase 3 trials of multi-TKI plus ICI combination therapy compared with sunitinib, increased risk for diarrhea, hypothyroidism, and rash was identified to be associated with the combination therapy. Similarly, in the analysis of clinical trial data from a variety of studies on multi-TKI monotherapy and multi-TKI plus ICI combination therapy, where the impact of adding ICIs to multi-TKIs was evaluated, hypothyroidism and rash were also identified as increased events in the combination therapy. Furthermore, the pooled incidence rates of anorexia, fatigue, and hand-foot syndrome decreased in the combination group with multi-TKI and ICI. Based on these results, the addition of ICIs to multi-TKI therapy would increase the risk of diarrhea, hypothyroidism, and rash compared with multi-TKI monotherapy. Simultaneously, it was suggested that the addition of ICI would decrease the risk of AEs related to performance status, presumably because of enhanced efficacy.

Our systematic review and analysis indicated that the incidence rates of diarrhea, hypothyroidism, and rash were increased by adding ICIs to multi-TKIs, but these events have been reported as common AEs in ICI monotherapy. As for diarrhea, colitis has been known as an immune-related adverse event (irAE) caused by ICI monotherapy, and diarrhea could be developed as a symptom of colitis [36, 37]. Forty-four of 48 studies on multi-TKI monotherapy and 24 of 25 studies on multi-TKI plus ICI combination therapy reported diarrhea as a TRAE with an incidence rate of more than 10%. According to the results of RR against sunitinib, multi-TKI plus ICI combination

therapy increased the risk of diarrhea. Although diarrhea has been recognized as a side effect of multi-TKI monotherapy, appropriate measures should be taken for multi-TKI plus ICI combination therapy because the addition of ICI could further increase the risk of diarrhea.

In hypothyroidism, the thyroid is one of the organs associated with the immune system, and some autoimmune diseases can develop because of thyroid abnormalities. Therefore, hypothyroidism is clearly one of the side effects associated with ICIs and has already been reported as a common irAE for ICI monotherapy [38]. In this study, 22 of 25 studies on multi-TKI plus ICI combination therapy presented hypothyroidism as a TRAE, with an incidence rate of more than 10%. On the contrary, in the studies on multi-TKI monotherapy, the number of studies with more than 10% incidence rate of treatment-related hypothyroidism differed depending on the multi-TKI compound. Therefore, it should be considered whether the combination therapy of multi-TKI and ICI increases the risk of hypothyroidism additively or synergistically.

Rash is also one of the side effects related to the immune system and is a well-known irAE of ICI monotherapy [39]. It has been reported that irAEs, such as disorders of the skin, endocrine organ, and gastrointestinal tract could be predictors of the efficacy of ICI monotherapy. [40]. In the present study, 17 of 48 studies on multi-TKI monotherapy and 19 of 25 studies on multi-TKI plus ICI combination therapy presented rash as a TRAE with an incidence rate of more than 10%. Rash was reported most frequently with regorafenib in seven studies. In addition, some multi-TKI plus ICI combination therapies showed more than two-fold increase in RR of rash against sunitinib; the RR differed depending on the type of combination of multi-TKI and ICI. Therefore, it should also be considered whether the combination therapy of multi-TKIs and ICIs causes an increased risk of rash additively or synergistically. Overall, the risk of these AEs could be increased by adding ICIs to multi-TKI monotherapy. It is important to discuss these AEs with specialists early and to take appropriate measures.

The pooled incidence rates of anorexia, fatigue, and hand-foot syndrome were decreased by the addition of ICIs to multi-TKI monotherapy. The results of health-related quality of life in previous phase 3 trials indicated improved performance

status of multi-TKI plus ICI combination therapy compared with multi-TKI monotherapy [41, 42]. Although the results of the present study should be interpreted with caution because of limited data, the improvement in AEs related to quality of life was consistent with the previous reports.

Our study had several limitations. First, only TRAE data with > 10% incidence rates were collected in this study. Second, the type of cancer was not specified in this study, and clinical studies on various types of cancer were included in the analyses. However, data on TRAEs were collected to minimize the influence of using data for various types of cancer on the analyses. Finally, because several types of multi-TKIs and ICIs were analyzed together, the results of this study are highly heterogeneous.

In conclusion, our systematic review and analysis identified diarrhea, hypothyroidism, and rash as TRAEs leading to increased toxicities with multi-TKI plus ICI combination therapy compared with multi-TKI monotherapy. Additionally, some AEs related to performance status were improved by the addition of ICIs to multi-TKIs. The results of the present study are expected to optimize the management of toxicities caused by multi-TKI plus ICI combination therapy in individual patients, as the number of clinical studies using this combination therapy and opportunities for their use in clinical practice are expected to increase. As this study was conducted based on the results of limited clinical studies, further investigation is needed based on the accumulating results of future clinical studies and real-world data.

4. Overall Discussion

In this research, we examined the ways of risk mitigation in terms of safety management for subjects in clinical development of anti-cancer drugs. Based on the results of Research 1, it was indicated that pathognomonic AEs for signal inhibitor agents can be identified earlier in the development process than those for ICIs. Especially for ICIs, effective measures such as establishment of a management structure in the institution and/or guidance and collaboration with appropriate specialists are important for proper toxicity management. To mitigate the risk of toxicity associated with combination therapy, it is considered necessary to evaluate the safety of the combination therapy from early phase. It was also found that the higher the number of subjects in phase 1 trials, the greater the predictability of AEs in the later trials. Therefore, if a large-scale study is planned to be conducted shortly after a phase 1 trial, setting up an expansion cohort in the phase 1 trial would be an option to ensure sufficient safety information.

ICIs and combination therapy were revealed to pose a great challenge for toxicity management in Research 1. Therefore, in Research 2, we focused on combination therapy of multi-TKI and ICI, which has been attracting great attention recently, to examine countermeasures, and found that multi-TKI plus ICI combination therapy increased risk for diarrhea, hypothyroidism, and rash compared with sunitinib monotherapy. In the analysis of clinical trial data from a variety of studies on multi-TKI monotherapy and multi-TKI plus ICI combination therapy, hypothyroidism and rash were also identified as increased AEs in the combination therapy. It is necessary to understand that the incidence of these AEs increases in the combination therapy of multi-TKI plus ICI, and collaboration with specialist physicians and management of the AEs as early as possible are important.

Cancer is a disease directly linked to the survival of patients, and development of novel therapeutic drugs for patients with high unmet medical need is urgent. To achieve early approval of new anti-cancer drugs, their fundamental safety profile must be evaluated based on clinical trial data from a small number of subjects. However, severe AEs could be identified only after prescribing the drug to a larger population, so considering the risks and benefits of the drug sufficiently is important in aiming the

early approval. Based on the results of Research 1 and 2, we identified several factors to be considered in toxicity management, and proposed measures to be taken for risk mitigation. Recently, drugs with various modalities are being developed with various clinical development strategies. It is required to conduct benefit and risk assessments at the time of development planning and to draw up a development strategy with patient safety as the highest priority. When aiming for early approval, it is important to consider appropriate toxicity management based on the development strategy and characteristics of the drug, making the best use of safety data obtained until then including those of drugs with the same pharmacological class. In such a situation, the results of this research such as easiness to specify safety profiles, degree of risk, and preventive measures should be served as a useful reference. At the same time, limitations of identifying the safety profile based on data from a small number of patients should also be understood, and continued efforts should be made to obtain further safety data in the post-marketing stage.

We expect that our research will contribute to designing a strategy of risk mitigation for better addressing the challenges of securing subject safety in the early development phase.

5. Conclusion

Toxicity management is relatively straightforward for anti-cancer drugs of which AEs associated with the mechanism of action are known; While pathognomonic AEs for signal inhibitor agents can be identified earlier in the development process, ICIs and combination therapy could pose a huge challenge in toxicity management. Collaboration with not only oncologists but also appropriate specialists is needed. In clinical development of combination therapy with other drugs, safety assessment of the combination therapy at early phase is considered significant for understanding the toxicity profile. In case of the presence of precedent trials with the same pharmacological class of drugs, their safety data can be a useful reference. A stepwise development strategy should be considered to mitigate the risk.

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7. Acknowledgement

I would like to express my deep and sincere gratitude to Professor Mamoru Narukawa for giving me the opportunity to do my research and providing invaluable guidance throughout this study. His insight, vision, sincerity and motivation have deeply inspired me. It was a great privilege and honor to study under his guidance. I am also grateful to Assistant Professor Masayuki Kaneko for his assistance on my research. I have greatly benefited from his insightful suggestions and warm encouragements. I am confident that I would never have accomplished my research without his tremendous support.

I would like to thank Professor Yuji Yoshiyama, Professor Mitsuo Tanabe, and Associate Professor Mitsuhiro Sugawara for their reviews and helpful discussion on this study. Their constructive comments and discussions were illuminating and were definitely the key part of components forming this work.

I would like to offer my special thanks to Ms. Yukiko Minami for her generous support on my student life at Kitasato university. Also, my special appreciation goes to the classmates at department of Clinical Medicine (Pharmaceutical Medicine). I have learned a lot from them, and they have been motivating and encouraging me. Their support and inspiration made my days exceptional moment. I wish the best of luck for their research and career.

Lastly, I would like to express my profound gratitude to my family and friends who have been supporting and encouraging me throughout the years at Kitasato university. Their moral and continuing support considerably helped me keep myself motivated.

8. Appendix

Table 8 Supplementary Table. Characteristics of phase 1 and 3 trials

Drug	Types of phase 1 and 3 trials	Number of subjects	Total number of subjects in phase 1 trials	Total number of phase 1 trials	Tumor type
Aflibercept	1	16	16	1	Colorectal cancer
	3	611			Colorectal cancer
Regorafenib	1	15	187	4	Solid tumor
	1	84			Solid tumor
	1	76			Solid tumor
	1	12			Solid tumor
	3	500			Colorectal cancer
Olaparib	1	23	121	2	Solid tumor
	1	98			Solid tumor
	3	195			Ovarian cancer
	3	205			Breast cancer
Inotuzumab ozogamicin	1	30	78	2	Non-Hodgkin lymphoma
	1	48			Non-Hodgkin lymphoma
	3	164			Leukemia
Trastuzumab emtansine	1	52	62	2	Breast cancer
	1	10			Breast cancer
	3	490			Breast cancer
Atezolizumab	1	6	487	2	Solid tumor
	1	481			Solid tumor
	3	609			Lung cancer
Ponatinib	1	81	116	2	Chronic myeloid leukemia
	1	35			Chronic myeloid leukemia
	3	154			Chronic myeloid leukemia
Carfilzomib	1	26	150	4	Multiple myeloma
	1	11			Hematological cancer
	1	84			Multiple myeloma
	1	29			Hematological cancer
	3	392			Multiple myeloma
	3	157			Multiple myeloma
Vandetanib	1	14	32	2	Thyroid gland
	1	18			Solid tumor
	3	231			Thyroid gland

Drug	Types of phase 1 and 3 trials	Number of subjects	Total number of subjects in phase 1 trials	Total number of phase 1 trials	Tumor type
Ipilimumab	1	15	115	2	Lung cancer (NSCLC)
	1	100			Renal cell carcinoma
	3	547			Renal cell carcinoma
Lenvatinib	1	82	91	2	Solid and lymphoma
	1	9			Solid tumor
	3	261			Differentiated thyroid
Pomalidomide	1	38	95	3	Multiple myeloma
	1	12			Multiple myeloma
	1	45			Multiple myeloma
	3	300			Multiple myeloma
	3	167			Myelofibrosis
Ramucirumab	1	7	96	6	Breast cancer
	1	37			Solid tumor
	1	25			Solid tumor
	1	15			Solid tumor
	1	6			Gastric cancer
	1	6			Colorectal cancer
	3	327			Gastric cancer
	3	236			Gastric cancer
Vemurafenib	1	32	43	2	Melanoma
	1	11			Melanoma
	3	336			Melanoma
Alemtuzumab	1	6	181	4	Chronic Lymphocytic Leukemia
	1	68			Non-Hodgkin lymphoma or Chronic Lymphocytic Leukemia
	1	71			Non-Hodgkin lymphoma or Chronic Lymphocytic Leukemia
	1	36			Non-Hodgkin lymphoma or Chronic Lymphocytic Leukemia
	3	147			Chronic Lymphocytic

Drug	Types of phase 1 and 3 trials	Number of subjects	Total number of subjects in phase 1 trials	Total number of phase 1 trials	Tumor type
					Leukemia
Nivolumab	1	306	323	2	Solid tumor
	1	17			Solid tumor
	3	135			Lung cancer (SCLC)
	3	287			Lung cancer (NSCLC)
Cabazitaxel	1	48	73	2	Prostate cancer
	1	25			Solid tumor
	3	371			Prostate cancer
Abiraterone	1	27	81	2	Prostate cancer
	1	54			Prostate cancer
	3	542			Prostate cancer
Enzalutamide	1	47	187	2	Prostate cancer
	1	140			Prostate cancer
	3	800			Prostate cancer
Pazopanib	1	13	93	2	Solid tumor
	1	17			Solid tumor
	1	63			Solid tumor
	3	240			Malignant soft tissue tumor
Axitinib	1	12	18	2	Solid tumor
	1	6			Solid tumor
	3	356			Renal cell carcinoma
Fulvestrant	1	20	20	1	Breast cancer
	3	735			Breast cancer
Eribulin	1	32	68	3	Solid tumor
	1	21			Solid tumor
	1	15			Solid tumor
	3	503			Breast cancer
Temsirolimus	1	24	164	4	Solid tumor
	1	16			Solid tumor
	1	26			Solid tumor
	1	27			Solid tumor
	1	71			Renal cell carcinoma
	3	208			Renal cell carcinoma
	3	208			Renal cell carcinoma
Lenalidomide	1	27	42	2	Multiple myeloma
	1	15			Multiple myeloma
	3	177			Multiple myeloma
	3	176			Multiple myeloma
Dasatinib	1	18	18	1	Chronic myeloid leukemia

Drug	Types of phase 1 and 3 trials	Number of subjects	Total number of subjects in phase 1 trials	Total number of phase 1 trials	Tumor type
	3	662			Chronic myeloid leukemia
Bortezomib	1	53	170	5	Solid tumor
	1	43			Solid tumor
	1	27			Solid tumor
	1	31			Solid tumor
	1	16			Multiple myeloma
	3	331			Multiple myeloma
Daratumumab	1	32	152	4	Multiple myeloma
	1	9			Multiple myeloma
	1	8			Multiple myeloma
	1	103			Multiple myeloma
	3	243			Multiple myeloma
Sorafenib	1	53	53	1	Solid tumor
	3	207			Thyroid cancer
Pembrolizumab	1	10	874	3	Solid tumor
	1	276			Melanoma
	1	38			Lung cancer (NSCLC)
	1	550			Lung cancer (NSCLC)
	3	555			Melanoma
Durvalumab	1	22	22	1	Solid tumor
	3	475			Lung cancer
Obinutuzumab	1	12	12	1	Non-Hodgkin lymphoma
	3	194			Non-Hodgkin lymphoma
	3	698			Non-Hodgkin lymphoma

Table 9 Supplementary Table. Disagreement rate and agreement rate for each phase 3 trial

Drug	Number of subjects in phase 3 trials	Disagreement rate for each phase 3 trial	Agreement rate for each phase 3 trial
Aflibercept	611	42.1	34.2
Regorafenib	500	24.2	27.4
Olaparib	195	50.0	27.3
	205	31.3	18.8
Inotuzumab ozogamicin	164	56.3	29.6
Trastuzumab emtansine	490	15.0	17.5
Atezolizumab	609	33.3	14.3
Ponatinib	154	25.0	31.8
Carfilzomib	392	46.4	34.8
	157	48.6	26.4
Vandetanib	231	31.6	18.4
Ipilimumab	547	37.3	22.0
Lenvatinib	261	27.8	29.2
Pomalidomide	300	62.2	28.4
	167	52.5	13.6
Ramucirumab	327	23.8	27.4
	236	22.9	18.1
Vemurafenib	336	6.4	23.4
Alemtuzumab	147	20.9	18.6
Nivolumab	135	28.2	15.4
	287	37.8	13.3
Cabazitaxel	371	38.0	26.0
Abiraterone	542	51.5	18.2
Enzalutamide	800	55.2	31.0
Pazopanib	240	28.6	16.1
Axitinib	356	18.5	20.4
Fulvestrant	735	16.7	0.0
Eribulin	503	27.1	16.7
Temsirolimus	208	22.5	31.0
	208	26.7	38.7
Lenalidomide	177	64.0	18.0

Drug	Number of subjects in phase 3 trials	Disagreement rate for each phase 3 trial	Agreement rate for each phase 3 trial
	176	62.1	16.8
Dasatinib	662	13.5	10.8
Bortezomib	331	37.7	26.1
Daratumumab	243	38.0	28.0
Sorafenib	207	47.1	23.5
Pembrolizumab	555	9.1	9.1
Durvalumab	475	84.6	0.0
Obinutuzumab	194	69.6	7.1
	698	59.5	9.5

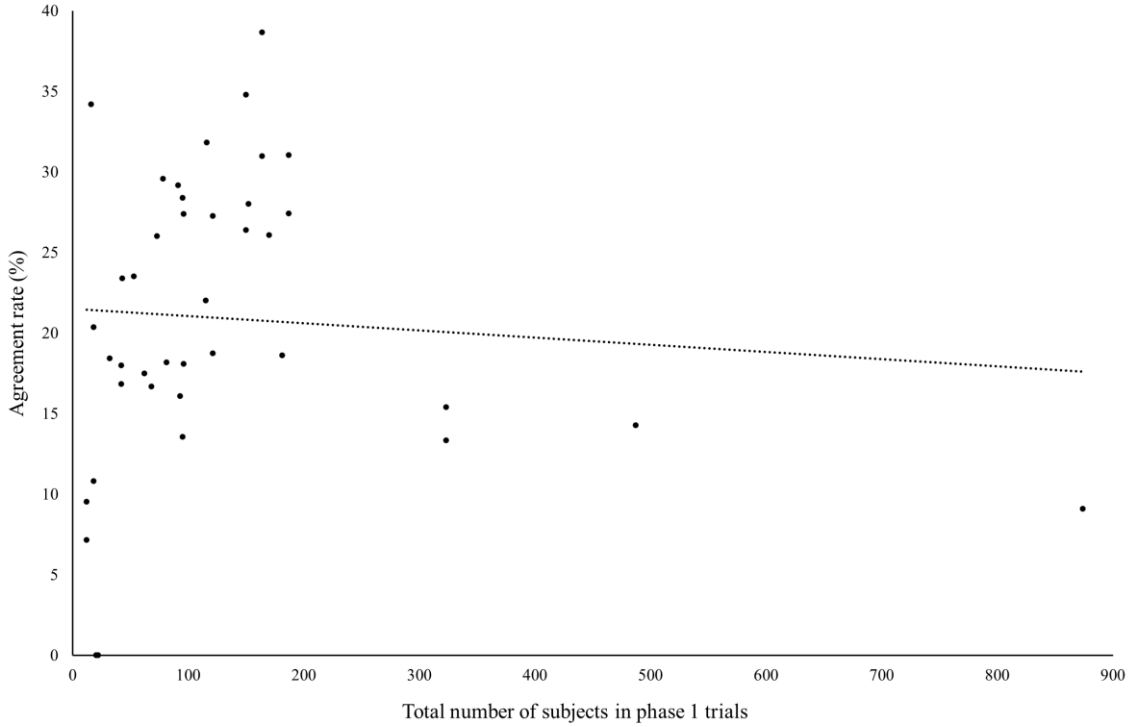


Figure 5 Supplementary Figure. Correlation between agreement rate for each phase 3 trial and total number of subjects in phase 1 trials in all anticancer drugs.

Table 10 Supplementary Table. List of the studies included in the analysis of treatment-related adverse events

Study	Ref	Trial name	Phase	Cancer type	Multi-TKI	ICI	Total patient number	Patients with any grade AEs	Patients with grade 3 or higher AEs
Multiple tyrosine kinase inhibitor monotherapy									
Li2010	43	N.A.	1	Solid tumor	Apatinib	N.A.	46	N.A.	N.A.
Liao2018	44	N.A.	2	CRC	Apatinib	N.A.	27	N.A.	N.A.
Wu2018	45	N.A.	2	NSCLC	Apatinib	N.A.	40	36	N.A.
Xu2019	46	N.A.	2	SCLC	Apatinib	N.A.	40	40	N.A.
Liu2020	47	N.A.	2	Chordoma	Apatinib	N.A.	29	N.A.	N.A.
Ma2020	48	N.A.	2	DLBCL	Apatinib	N.A.	32	N.A.	N.A.
Song2022	49	N.A.	2	Thymic epithelial	Apatinib	N.A.	25	25	15
Rixe2007	50	N.A.	2	RCC	Axitinib	N.A.	52	48	28
Motzer2013	51	AXIS	3	RCC	Axitinib	N.A.	359	N.A.	N.A.
Karam2014	52	N.A.	2	RCC	Axitinib	N.A.	24	N.A.	N.A.
Eto2014	53	N.A.	2	RCC	Axitinib	N.A.	64	N.A.	N.A.
Mcnamara2015	54	N.A.	2	HCC	Axitinib	N.A.	30	N.A.	N.A.
Swiecicki2015	55	N.A.	2	HNSCC	Axitinib	N.A.	42	N.A.	N.A.
Strosberg2016	56	N.A.	2	Neuroendocrine tumor	Axitinib	N.A.	30	N.A.	N.A.
Park2018	57	N.A.	2	RCC	Axitinib	N.A.	40	39	18

Study	Ref	Trial name	Phase	Cancer type	Multi-TKI	ICI	Total patient number	Patients with any grade AEs	Patients with grade 3 or higher AEs
Gross-G2018	58	ATLAS	3	RCC	Axitinib	N.A.	356	N.A.	N.A.
Hui2018	59	N.A.	2	Nasopharyngeal carcinoma	Axitinib	N.A.	40	N.A.	N.A.
Tsimafeyeu2019	60	FavorAx	2	RCC	Axitinib	N.A.	21	N.A.	N.A.
Negrier2020	61	AXIPAP	2	RCC	Axitinib	N.A.	44	43	24
Swiecicki2021	62	N.A.	2	HNSCC	Axitinib	N.A.	28	N.A.	N.A.
Kuzrock2011	63	N.A.	2	MTC	Cabozantinib	N.A.	86	77	N.A.
Neal2016	64	ECOG-ACRIN 1512	2	NSCLC	Cabozantinib	N.A.	40	N.A.	N.A.
Drilon2016	65	N.A.	2	NSCLC	Cabozantinib	N.A.	26	25	N.A.
Goyal2017	66	N.A.	2	Cholangiocarcinoma	Cabozantinib	N.A.	19	N.A.	N.A.
Rabinowits2018	67	N.A.	2	MCC	Cabozantinib	N.A.	8	N.A.	N.A.
Schoffski2020	68	EORTC1317	2	GIST	Cabozantinib	N.A.	50	48	34
Boxtel2022	69	N.A.	2	SGC	Cabozantinib	N.A.	25	N.A.	N.A.
Kelley 2022	70	COSMIC-312	3	HCC	Cabozantinib	N.A.	188	178	104
Boss2012	71	N.A.	1	Solid tumor	Lenvatinib	N.A.	82	N.A.	N.A.
Schlumberger2015	72	SELECT	3	Thyroid cancer	Lenvatinib	N.A.	261	254	198
Sato2020	73	REMORA	2	Thymic	Lenvatinib	N.A.	42	N.A.	N.A.

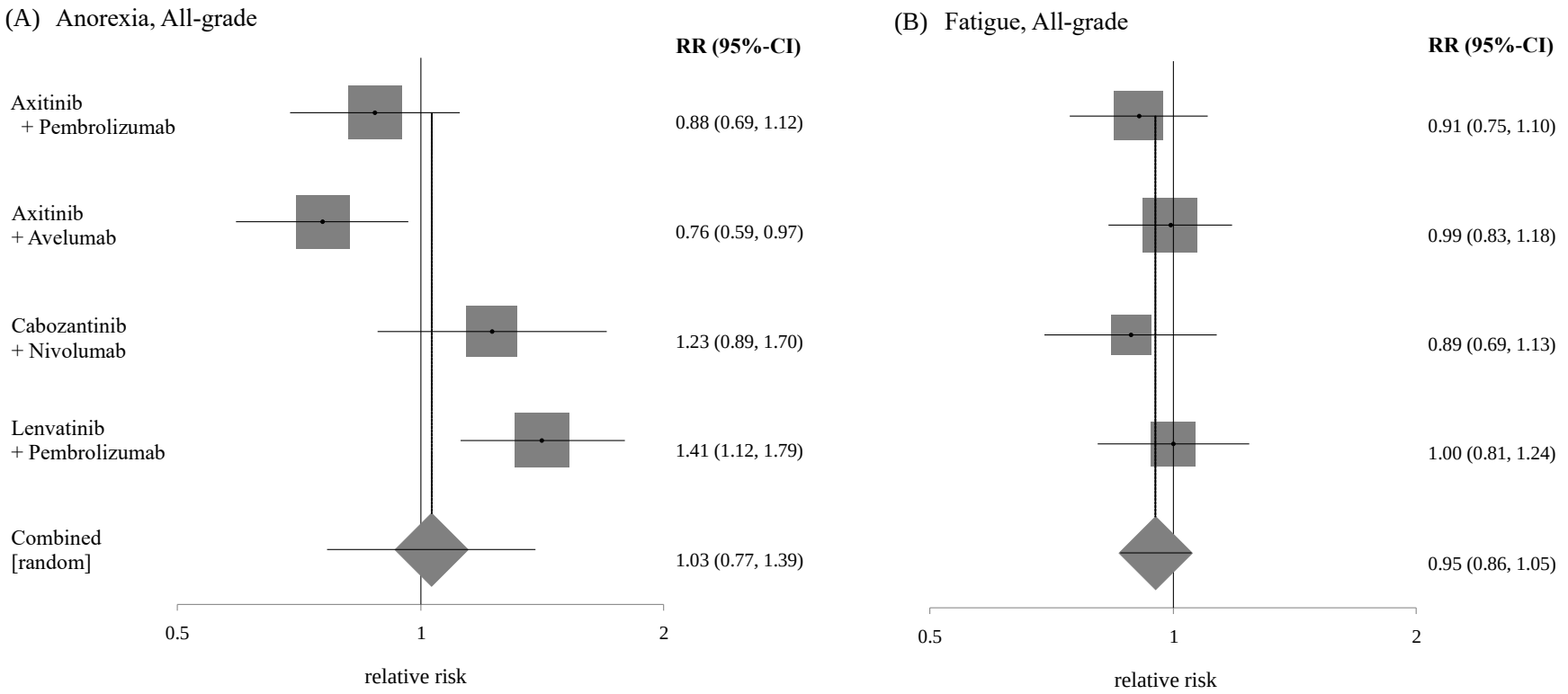
Study	Ref	Trial name	Phase	Cancer type	Multi-TKI	ICI	Total patient number	Patients with any grade AEs	Patients with grade 3 or higher AEs
				carcinoma					
Ueno2020	74	N.A.	2	BTC	Lenvatinib	N.A.	26	26	16
Vergote2020	75	N.A.	2	Endometrial cancer	Lenvatinib	N.A.	133	116	78
Liu2021	76	Study 108	1	Solid tumor	Lenvatinib	N.A.	12	N.A.	N.A.
Strumberg2012	77	N.A.	1	CRC	Regorafenib	N.A.	38	34	22
Demetri2013	78	GRID	3	GIST	Regorafenib	N.A.	132	130	81
Bruix2013	79	N.A.	2	HCC	Regorafenib	N.A.	36	35	21
Grothey2013	80	CORRECT	3	CRC	Regorafenib	N.A.	500	455	271
Sunakawa2014	81	N.A.	1	Solid tumor	Regorafenib	N.A.	15	15	N.A.
Li2015	82	CONCUR	3	CRC	Regorafenib	N.A.	136	132	74
Bruix2017	83	RESORCE	3	HCC	Regorafenib	N.A.	374	346	194
Davis2019	84	SARC024	2	Osteosarcoma	Regorafenib	N.A.	22	20	14
Lombardi2019	85	REGOMA	2	Glioblastoma	Regorafenib	N.A.	59	N.A.	N.A.
Kim2020	86	N.A.	2	BTC	Regorafenib	N.A.	39	N.A.	N.A.
Demols2020	87	REACHIN	2	BTC	Regorafenib	N.A.	33	26	12
Suzuki2020	88	RESET	2	CRC	Regorafenib	N.A.	68	68	39
Marrari2020	89	N.A.	2	Sarcoma	Regorafenib	N.A.	21	N.A.	N.A.
Aparicio2020	90	REGOLD	2	CRC	Regorafenib	N.A.	42	41	35

Study	Ref	Trial name	Phase	Cancer type	Multi-TKI	ICI	Total patient number	Patients with any grade AEs	Patients with grade 3 or higher AEs
Combination therapy of multiple tyrosine kinase inhibitor plus immune checkpoint inhibitor									
Xu2019	91	N.A.	1a/b	HCC, GC	Apatinib	Camrelizumab	43	N.A.	N.A.
Lan2020	92	CLAP	2	Cervical cancer	Apatinib	Camrelizumab	45	43	32
Liu2020	93	N.A.	2	TNBC	Apatinib	Camrelizumab	40	39	10
Cheng2021	94	CAP 01	2	GTN	Apatinib	Camrelizumab	20	18	12
Fan2021	95	PASSION	2	SCLC	Apatinib	Camrelizumab	59	56	43
Zhou2021	96	N.A.	1b/2	NSCLC	Apatinib	Camrelizumab	105	104	73
Xu2021	97	RESCUE	2	HCC	Apatinib	Camrelizumab	190	189	147
Meng2022	98	CAP 02	2	ESCC	Apatinib	Camrelizumab	52	41	23
Choueiri2018	99	JAVELN Renal 100	1b	RCC	Axitinib	Avelumab	55	53	32
Motzer2019	100	JAVELN Renal 101	3	RCC	Axitinib	Avelumab	434	414	246
Awada2020	101	GliAvAx	2	Glioblastoma	Axitinib	Avelumab	54	54	N.A.
Atkins2018	102	N.A.	1b	RCC	Axitinib	Pembrolizumab	52	51	33
Rini2019	103	KEYNOTE-426	3	RCC	Axitinib	Pembrolizumab	429	413	270
Agarwal2022	104	COSMIC-021	1b	CRPC	Cabozantinib	Atezolizumab	132	126	72
Kelley2022	70	COSMIC-312	3	HCC	Cabozantinib	Atezolizumab	429	399	236

Study	Ref	Trial name	Phase	Cancer type	Multi-TKI	ICI	Total patient number	Patients with any grade AEs	Patients with grade 3 or higher AEs
Marandino2021	105	ARCADIA	2	UC	Cabozantinib	Durvalumab	16	14	N.A.
Choueiri2021	106	CheckMate 9ER	3	RCC	Cabozantinib	Nivolumab	320	309	194
Makker2019	107	N.A.	2	Endometrial cancer	Lenvatinib	Pembrolizumab	53	49	36
Taylor2020	108	N.A.	1b/2	Solid tumor	Lenvatinib	Pembrolizumab	137	133	92
Kawazoe2020	109	EPOC1706	2	GC	Lenvatinib	Pembrolizumab	29	29	14
Lee2021	110	Study 111/ KEYNOTE-146	1b/2	RCC	Lenvatinib	Pembrolizumab	145	144	95
Motzer2021	111	CLEAR	3	RCC	Lenvatinib	Pembrolizumab	352	341	252
Makker2022	112	Study 309/ KEYNOTE-775	3	Endometrial cancer	Lenvatinib	Pembrolizumab	406	395	316
Fukuoka2020	113	REGONIVO/ EPOC1603	1b	GC, CRC	Regorafenib	Nivolumab	50	50	20
Kim2022	114	N.A.	1/1b	CRC	Regorafenib	Nivolumab	51	N.A.	26

Abbreviations: BTC, biliary tract cancer; CRC, colorectal cancer; CRPC, castration-resistant prostate cancer; DLBCL, diffuse large B cell Lymphoma; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; GIST, gastrointestinal stromal tumor; GTN, gestational trophoblastic neoplasia; HCC,

Study	Ref	Trial name	Phase	Cancer type	Multi-TKI	ICI	Total patient number	Patients with any grade AEs	Patients with grade 3 or higher AEs
hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; MCC, merkel cell carcinoma; MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; SCLC, small cell lung cancer; SGC, salivary gland cancer; TNBC, triple-negative breast cancer; UC, urothelial carcinoma									


(A) Anorexia, All-grade
RR (95%-CI)
Axitinib + Pembrolizumab
0.88 (0.69, 1.12)
Axitinib + Avelumab
0.76 (0.59, 0.97)
Cabozantinib + Nivolumab
1.23 (0.89, 1.70)
Lenvatinib + Pembrolizumab
1.41 (1.12, 1.79)
Combined [random]
1.03 (0.77, 1.39)
0.5
1
2
relative risk
(B) Fatigue, All-grade
RR (95%-CI)
0.91 (0.75, 1.10)
0.99 (0.83, 1.18)
0.89 (0.69, 1.13)
1.00 (0.81, 1.24)
0.95 (0.86, 1.05)
0.5
1
2
relative risk

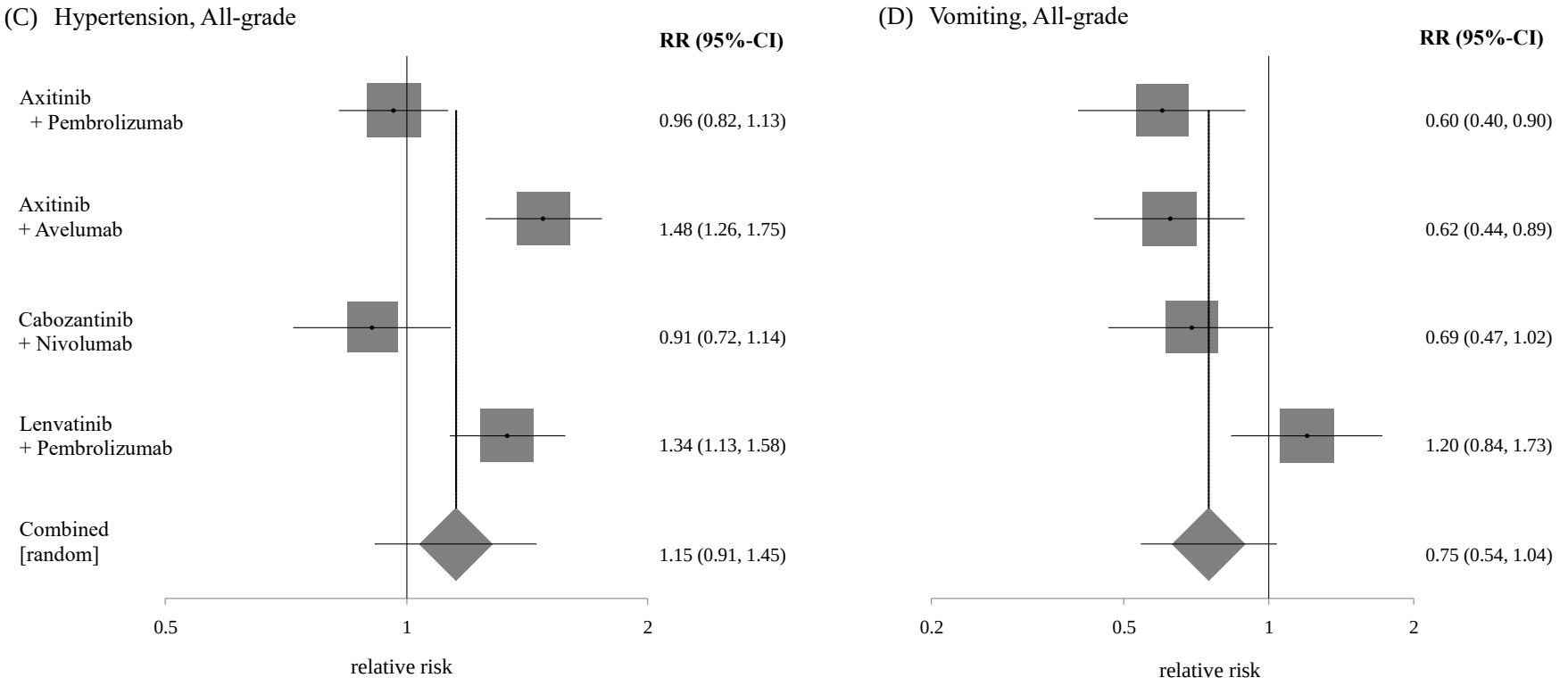


Figure 6 Supplementary Figure. Forest plot of relative risk of adverse events (all grade) for (A) anorexia, (B) fatigue, (C) hypertension and (D) vomiting for immune checkpoint inhibitors plus multiple tyrosine kinase inhibitor compared with that of sunitinib.

Abbreviations: RR, relative risk