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REVIEW

Global trends in the distribution of cancer types among patients in oncology phase I trials, 1991–2015

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Summary

Background Systematic analyses regarding cancer types of patients enrolled in oncology phase I trials are scarce. The global distribution, time-dependent change, and regional differences were evaluated. *Methods* A systematic search of the PubMed database, in which all single-agent phase I trials permitting the enrollment of all-comer patients with any type of solid tumor published between January 1991 and December 2015 were specified, was performed. Trials expected to enroll specific patient populations were excluded according to predefined criteria. *Results* Eight hundred and sixty-six eligible trials, which had enrolled 29,112 advanced solid tumor patients, were identified. Colorectal ($n = 7510$; 25.8%) and lung cancer ($n = 3212$; 11.0%) were the most prevalent solid tumors, followed by sarcoma ($n = 1756$; 6.0%), breast cancer ($n = 1623$; 5.6%), and renal cancer ($n = 1589$; 5.5%). The proportion of patients with either colorectal or lung cancer tended to decrease over time. The proportion of trials, in which patients with either of these two cancers accounted for ≥50.0% of the total number of patients in each trial, also decreased: 33 of 67 trials (31/67) (46.3%) in 1991–1995, 58/142 (40.8%) in 1996–2000, 59/223 (26.5%) in 2001–2005, 38/189 (20.1%) in 2006–2010, and 41/245 (16.7%) in 2011–2015. Instead, the proportion of patients with various types of cancer increased, leading to diversification of enrolled patients. *Conclusions* The distribution of cancer types among patients in phase I trials has changed. The comprehensive review of the distribution of solid tumor types could contribute to flexible trial designs and optimal patient recruitment.

Keywords Phase I trial · Cancer · Cancer type · Global trend

Introduction

Phase I oncology trials are an important first step to expand preclinical research into clinical practice. Traditionally, the main purpose of these trials has been to obtain the toxicity profile of new therapeutic agents and to determine the maximum tolerated dose and recommended dose for future clinical trials [1]. Preliminary assessment of efficacy has typically been the secondary purpose, which has allowed patients with any type of solid tumor (i.e., all-comers) to participate in these trials.

Recently, molecularly targeted agents and immunotherapeutic oncology drugs have become an important part of cancer treatment and the emergence of these therapies has been changing the traditional clinical trial design [2, 3]. The increased attention that is now paid to the evaluation of predictive biomarkers in early clinical trial settings allows for earlier identification of patients likely to benefit from new treatments. Prescreening strategies, in which patients are enrolled based on the molecular characteristics of their tumors, are frequently being adopted to establish proof-of-concept earlier and to support subsequent clinical trials (i.e., enriched-design clinical trials) [4–7]. A recent report from investigators at The University of Texas M. D. Anderson Cancer Center [8] stated that matched experimental targeted agents may be a better choice for patients with matched molecular alterations even in phase I trial settings and supported the use of biomarker-driven phase I trials [9]. Phase I trial designs have also started to change, with a greater emphasis on early hypothesis testing of investigational drugs [10, 11]. This personalized approach to oncology treatment and widespread clinical use of genome

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sequencing has enabled clinicians to pursue greater clinical benefits from phase I trials [12]. On the other hand, the traditional histological classification of cancer continues to incorporate molecular characteristics and trials for patients with a rare molecular alteration are required more urgently. An increasing number of phase I trials require enrollment of a specific patient population, including patients with rarer types of cancer, both in terms of histology and molecular alterations, and trial designs have become more complicated and recruitment of appropriate candidates more difficult [13]. Oncology phase I trials are undergoing change, but detailed information on cancer types of enrolled patients in phase I trials is insufficient.

In this study, we evaluated global trends in the types of cancer of enrolled patients in phase I trials, including time-dependent changes and regional differences in North America, Europe, and Asia. Since trials with an enriched-design would skew our data, trials included in this study were limited to all-comer phase I trials and trials expected to enroll specific patient populations were excluded according to criteria developed for this study. Comprehension of the distribution of enrolled patients will aid in the design of flexible phase I trials and will optimize the recruitment of patients for participation in these studies. Greater quality information on this topic will additionally be useful for reconsidering the appropriate time to introduce phase I trials.

Methods

The PubMed database was searched to identify articles on all-comer phase I clinical trials. All-comer phase I clinical trials were defined as trials in which patients with any type of solid tumor could be registered. Inclusion and exclusion criteria were defined to remove trials that tended to enroll patients with a specific type of cancer.

Search strategy and study selection

To search for phase I oncology trials, a combination of Medical Subject Headings (MeSH) terms and keywords were applied in the search toolbar ("neoplasms" [MeSH Terms] OR "cancer" [All Fields] OR "tumor" [All Fields] OR "tumour" [All Fields] OR "malignancy" [All Fields]). "Clinical trials, phase I," "Publication dates from January 1, 1991 to December 31, 2015," and "Humans" were selected as additional filters. Two independent investigators (K.I. and T.K.) individually assessed the titles and abstracts of articles identified by this search strategy and specified articles concerning all-comer phase I trials. The inclusion criteria included phase I trials of single-agent antineoplastic drugs against solid tumors in adult patients that were published in English and were not limited to patients with a specific type of cancer. Following the initial selection of abstracts, the full-texts were read, and trials were excluded if (a) they were for a new formation, treatment schedule, or dosage of an antineoplastic agent that has already been approved; (b) they re-evaluated a drug that has already been approved for cancer treatments in other nations; (c) they were of immunotherapeutic drugs or combination therapies with granulocyte-colony stimulating factor; (d) they involved non-systemic routes of administration (i.e., topical administration); (e) they recruited patients with a specific type of tumor histology or prescreened for enrollment with a diagnostic test to determine the presence of a predictive biomarker, such as a genomic alteration or immunohistochemical overexpression of a protein; (f) they included an expansion cohort that evaluated antitumor efficacy in a subpopulation of patients with a specific tumor histology and/or a specific molecular characteristic (if the number of patients in the expansion cohort were reported separately, the trial and patients not in the expansion cohort were included for analysis); (g) they evaluated patients with a specific organ abnormality; (h) they comprised <3 types of cancer; (i) patient enrollment was obviously biased; (j) insufficient data were available concerning the number of enrolled patients; or (k) the full-text was unavailable. Discrepancies between K.I. and T.K. were resolved through discussion and adjudication by a third investigator (N.Y.).

This retrospective study was approved by the Ethics Committee of the National Cancer Hospital (Tokyo, Japan).

Table 1 Characteristics of the 866 published phase I clinical trials

	Trials analyzed (n = 866)	Trials included (n = 1351)
Publication year, No. (%) of trials		
1991–1995	67 (7.7)	134 (9.9)
1996–2000	142 (16.4)	240 (17.8)
2001–2005	223 (25.8)	310 (22.9)
2006–2010	189 (21.8)	301 (22.3)
2011–2015	245 (28.3)	366 (27.1)
Location, No. (%) of trials		
North America	481 (55.5)	NA
Europe	241 (27.8)	NA
Asia	91 (10.5)	NA
Japan	73 (8.4)	NA
Multi-continent	40 (4.6)	NA
Other	13 (1.5)	NA
No. of patients per trial, mean (range)		
North America	30 (6–110)	NA
Europe	32 (6–108)	NA
Asia	18 (6–71)	NA
Multi-continent	44 (11–111)	NA

NA not applicable

Data extraction

Data collection was based only on the contents of the publications. Trial characteristics were extracted from all articles that met the inclusion and exclusion criteria, including the number of enrolled patients, first year of subject enrollment, publication year, primary site or tumor histology, drug name, and geographical location (North America, Europe, Asia, Multi-continent, or other).

Statistical analyses

The 25-year study period was subdivided into 5-year quintiles for reporting purposes. Temporal trends in the proportions of each cancer type were analyzed using the Cochran-Armitage trend test. Statistical analyses were performed using JMP Pro software version 13.0 (SAS Institute Inc., Cary, NC, USA). *P*-values below 0.05 were considered statistically significant.

Results

Composition of the final sample

A total of 10,596 titles and abstracts were reviewed, with 1351 articles meeting the inclusion criteria. The full-texts of all 1351 articles were carefully investigated and 866 eligible articles were identified that satisfied the predefined inclusion and exclusion criteria (Supplementary Fig. S1**)**. These studies enrolled a total of 29,112 patients. The clinical characteristics of the 866 all-comer phase I trials are summarized in Table 1. All extracted trials in our analysis were performed in North America (55.5%), Europe (27.8%), Asia (10.5%), multi-continents (4.6%), or other regions (1.5%). The median number of patients per trial was 30 (range, 6–110) in North America, 32 (range, 6–108) in Europe, and 18 (range, 6–71) in Asia. Of the total enrolled patients, patients with colorectal cancer ($n = 7510$; 25.8%) accounted for the largest proportion, followed by those with lung cancer ($n =$

Table 2 Trends in the cancer types of enrolled patient according to the period of study

Cancer Type	Publication Year, No. (%) of Patients						*P*-value [a]
	1991–1995	1996–2000	2001–2005	2006–2010	2011–2015	Total	
Colorectal	600 (27.7)	1317 (31.4)	2017 (26.9)	1512 (23.7)	2064 (23.2)	7510 (25.8)	<.001*
Lung [b]	350 (16.2)	521 (12.4)	801 (10.7)	673 (10.6)	867 (9.8)	3212 (11.0)	<.001*
Sarcoma [c]	100 (4.6)	247 (5.9)	439 (5.9)	446 (7.0)	524 (5.9)	1756 (6.0)	.04*
Breast	136 (6.3)	209 (5.0)	425 (5.7)	317 (5.0)	536 (6.0)	1623 (5.6)	.44
Renal	85 (3.9)	189 (4.5)	610 (8.1)	439 (6.9)	266 (3.0)	1589 (5.5)	<.001*
Ovarian/peritoneal	167 (7.7)	249 (5.9)	375 (5.0)	237 (3.7)	445 (5.0)	1473 (5.1)	<.001*
Melanoma	69 (3.2)	173 (4.1)	284 (3.8)	331 (5.2)	462 (5.2)	1319 (4.5)	<.001*
Pancreatic	59 (2.7)	132 (3.1)	229 (3.1)	260 (4.1)	410 (4.6)	1090 (3.7)	<.001*
Head & neck [d]	134 (6.2)	123 (2.9)	251 (3.3)	227 (3.6)	248 (2.8)	983 (3.4)	<.001*
Prostate	33 (1.5)	61 (1.5)	200 (2.7)	234 (3.7)	308 (3.5)	836 (2.9)	<.001*
Gastric	41 (1.9)	85 (2.0)	137 (1.8)	85 (1.3)	155 (1.7)	503 (1.7)	.14
Esophageal	11 (0.5)	31 (0.7)	99 (1.3)	132 (2.1)	184 (2.1)	457 (1.6)	<.001*
Mesothelioma	21 (1.0)	69 (1.6)	139 (1.9)	121 (1.9)	89 (1.0)	439 (1.5)	.07
Urothelial [e]	26 (1.2)	39 (0.9)	56 (0.7)	79 (1.2)	143 (1.6)	343 (1.2)	.001*
Liver	20 (0.9)	41 (1.0)	77 (1.0)	94 (1.5)	78 (0.9)	310 (1.1)	.90
Phase I uncommon [f]	74 (3.4)	214 (5.1)	438 (5.8)	582 (9.1)	998 (11.2)	2306 (7.9)	<.001*
Primary site unknown	238 (11.0)	500 (11.9)	916 (12.2)	606 (9.5)	1103 (12.4)	3363 (11.6)	.63

* $P < 0.05$

[a] Results from the Cochran-Armitage test

[b] Lung cancer included non-small cell lung cancer and small-cell lung cancer

[c] Sarcoma included all sarcomas except gastrointestinal stromal tumors

[d] Head & neck cancer included cancers arising in the lip, oral cavity, pharynx, larynx, and paranasal sinuses. Salivary gland and thyroid cancers were not included

[e] Urothelial cancer included bladder, ureter, and renal pelvis cancers

[f] Represents uncommon cancers, with each type accounting for <1.0% of the total. Large categories of cancer types in original articles were classified as they were in this analysis. For example, when the ambiguous term "head & neck cancer" was used in original articles and detailed information was not available, it was not certain whether the term meant with or without salivary gland or thyroid cancer. Therefore, we classified it into "head & neck cancer" for analysis in this study

3212; 11.0%), sarcoma ($n = 1756$; 6.0%), breast cancer ($n = 1623$; 5.6%), renal cancer ($n = 1589$; 5.5%), ovarian/peritoneal cancer ($n = 1473$; 5.1%), melanoma ($n = 1319$; 4.5%), pancreatic cancer ($n = 1090$; 3.7%), head and neck cancer ($n = 983$; 3.4%), prostate cancer ($n = 836$; 2.9%), gastric cancer ($n = 503$; 1.7%), esophageal cancer ($n = 457$; 1.6%), mesothelioma ($n = 439$; 1.5%), urothelial cancer ($n = 343$; 1.2%), and liver cancer ($n = 310$; 1.1%) (Table 2, Fig. 1a). We defined these 15 cancers, which account for >1.0% of all enrolled patients as phase I common cancers, and conducted further analyses.

The distributions of cancer types in phase I trials, cancer incidences, and cancer mortalities

The distribution of cancer types that have been included in phase I trials throughout the world (Fig. 1a), in North America over the past 10 years (Fig. 1b), the distribution of cancer incidence in the United States in 2015 (Fig. 1c), and the distribution of cancer mortalities in the United States in 2015 (Fig. 1d) are shown. The distributions of cancer types in phase I trials, of cancer incidences, and of cancer mortality have substantially differed.

Phase I common cancers

Figure 2 and Table 2 reveal changes in the proportions of the 15 phase I common cancers between 1991 and 2015. The study period was stratified into 5-year quintiles, according to the publication year because only approximately 40% of articles reported the first year of subject enrollment. The proportions of patients with colorectal or lung cancer tended to decrease: 27.7 and 16.2% in 1991–1995; 31.4 and 12.4% in 1996–2000; 26.9 and 10.7% in 2001–2005; 23.7 and 10.6% in 2006–2010; and 23.2 and 9.8% in 2011–2015, respectively. The proportions of patients with ovarian/peritoneal or head and neck cancer had also decreased. Conversely, the proportions of patients with melanoma, pancreatic

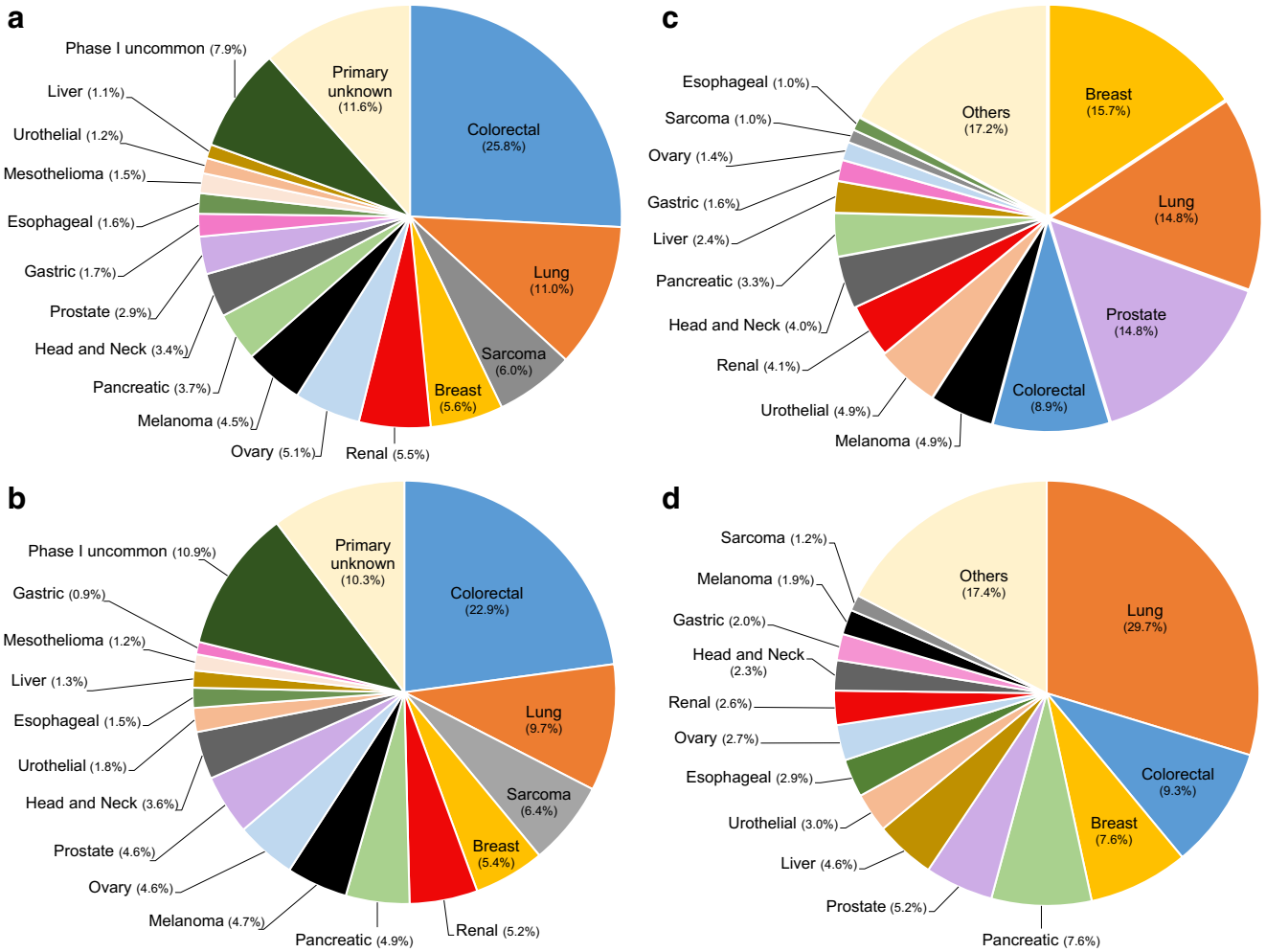


Fig. 1 The distributions of cancer types in phase I trials, cancer incidences, and cancer mortalities were shown. **a** The distribution of cancer types in phase I trials in the world in 1991–2015. **b** The distribution of cancer types in phase I trials in North America in 2006–2015. **c** The distribution of cancer incidence in the United States in 2015. **d** The distribution of cancer mortality in the United States in 2015

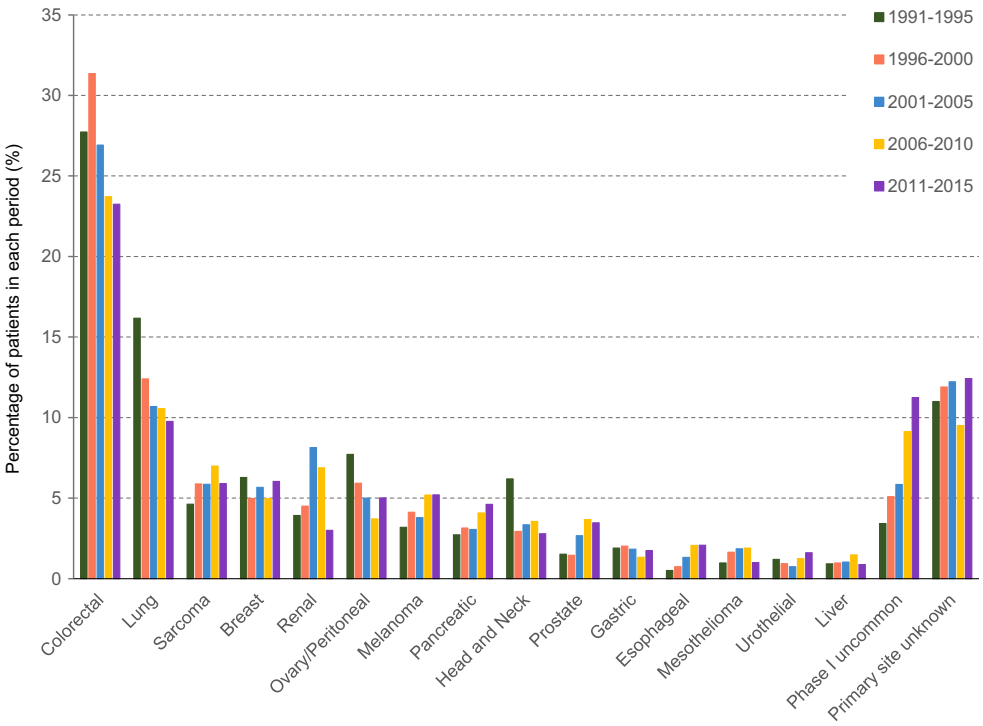


Fig. 2 Temporal Changes in the Proportions of the 15 Most Frequently Encountered Types of Cancer. The y-axis represents the proportion of patients with each type of cancer in each period of study

cancer, prostate cancer, esophageal cancer, and urothelial cancer had increased.

Two phase I major cancers

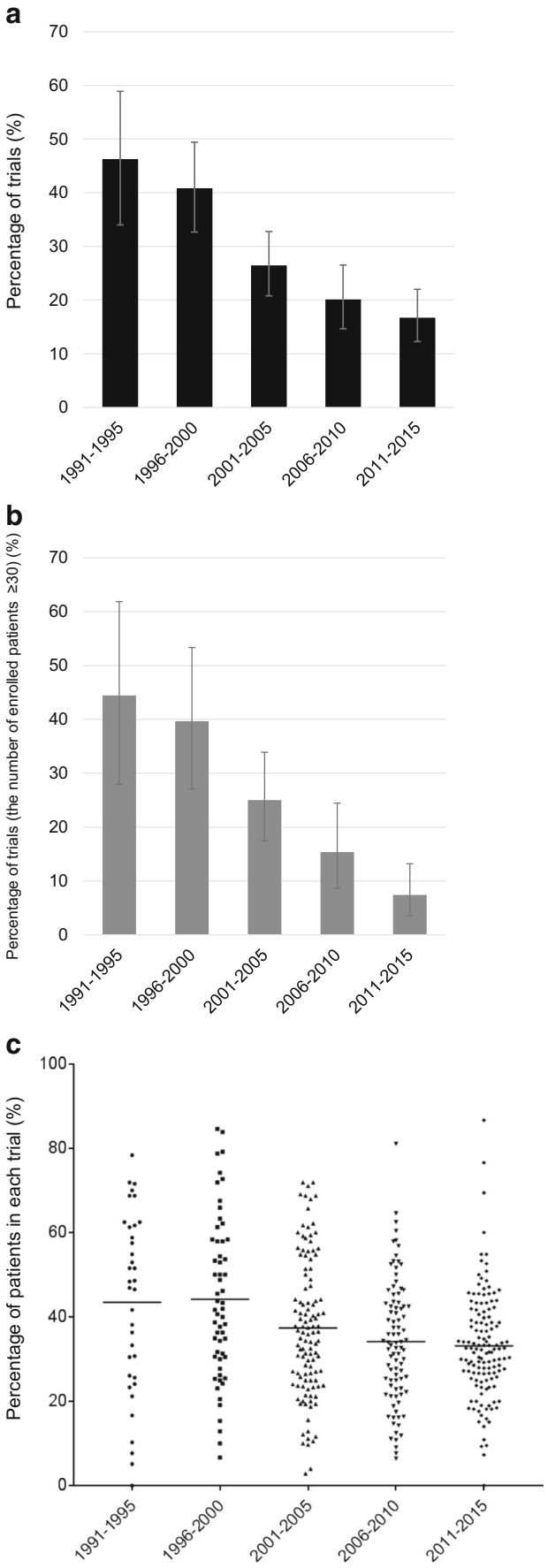
A large population of patients in phase I trials comprised those with colorectal or lung cancer. These two cancers were defined as "two phase I major cancers" and further analysis was conducted. The proportion of patients with these two phase I major cancers in each trial was calculated. Trials were specified in which the distribution of enrolled patients was imbalanced and the study population consisted of a majority of patients with these two cancers. The proportion of trials, in which patients with these two cancers accounted for ≥50.0% of the total enrolled patients in each trial, had decreased significantly: 31/67 (46.3%) in 1991–1995, 58/142 (40.8%) in 1996–2000, 59/223 (26.5%) in 2001–2005, 38/189 (20.1%) in 2006–2010, and 41/245 (16.7%) in 2011–2015 (Fig. 3a). In the trials that contained ≥30 enrolled patients, 16/36 (44.4%), 23/58 (39.7%), 29/116 (25.0%), 14/91 (15.4%), and 10/135 (7.4%), respectively (Fig. 3b, c).

Phase I uncommon cancers

As demonstrated in Fig. 1, the proportion of patients with phase I uncommon cancers (excluding the aforementioned 15 most frequently encountered cancer types) had increased: patients with each phase I uncommon cancer accounted for <1.0% of the total 29,112 patients. The total proportion of patients with phase I uncommon cancers in 1991–1995, 1996–2000, 2001–2005, 2006–2010, and 2011–2015 was 3.4%, 5.1%, 5.8%, 9.1%, and 11.2%, respectively. Time-dependent changes in the proportion of patients with each of the 16th to 25th most frequently encountered cancer types were as follows: The proportion of patients with thyroid cancer, neuroendocrine tumor, bile duct cancer, endometrial cancer, gastrointestinal stromal tumor, thymic tumor, salivary gland cancer and adrenal cancer had increased, while the proportion of patients with cervical cancer and central nervous system tumor did not change (Supplemental Table S1).

Regional trends and differences

The five most frequently encountered cancer types in each region in the past 10 years were as follows: colorectal cancer (22.9%), lung cancer (9.7%), sarcoma (6.4%), breast cancer (5.4%), and renal cancer (5.2%) in North America; colorectal cancer (25.8%), melanoma (7.8%), lung cancer (6.7%), sarcoma (6.6%), and breast cancer (5.6%) in Europe; and colorectal cancer (23.6%), lung cancer (21.6%), sarcoma (7.5%), breast cancer (6.9%), and gastric cancer (5.0%) in Asia (Supplemental Table S2). The differences in cancer types between these three regions over the past 10 years are summarized in Fig. 4. The distributions were relatively similar in North America and Europe, but differed in Asia. The proportion of patients with lung cancer, gastric cancer, and esophageal cancer was higher in Asia than in North America or Europe, whereas the proportion of patients with renal cancer, ovarian/peritoneal cancer, melanoma, pancreatic cancer, prostate cancer, urothelial cancer, and liver cancer was lower. The



◀ **Fig. 3** The Proportion of Trials That Comprised a Majority of Patients With the Two Phase I Major Cancers. The proportion of trials, in which patients with either colorectal or lung cancer accounted for ≥50.0% of the total number of patients in each trial, were calculated in each period of study. Error bars show 95% confidence intervals. **a** All 866 trials combined and (**b**) trials with ≥30 enrolled patients in each trial. **c** Beeswarm plot of the proportion of patients with either colorectal of lung cancer in each trial (with ≥30 enrolled patient)

proportion of patients with lung cancer had decreases in all three regions (Supplemental Table S3), whereas the proportion of patients with colorectal cancer had decreased solely in North America.

From the perspective of trials that comprised a majority of patients with the two phase I major cancers, the proportion of trials tended to decrease in the three regions: 22/42 (52.4%) in 1991–1995, 32/79 (40.5%) in 1996–2000, 38/140 (27.1%) in 2001–2005, 14/103 (13.6%) in 2006–2010, and 16/117 (13.7%) in 2011–2015 in North America; 7/23 (30.4%), 20/52 (38.5%), 16/69 (23.2%), 8/51 (15.7%), and 3/46 (6.5%) in Europe; 2/2 (100.0%), 3/3 (100.0%), 5/9 (55.6%), 14/20 (70.0%), and 21/57 (36.8%) in Asia. Although the imbalance in the distribution of enrolled patients was consistent in all three regions, it was more apparent in Asia than in Europe and North America. Many phase I trials in Asia were performed in Japan and these results in Asia mainly reflect the characteristics of trials conducted in Japan (Table 1).

Discussion

Our report is the first comprehensive review of cancer types observed among patients enrolled in all-comer phase I trials conducted globally between 1991 and 2015. Although some investigators have referred to the distribution at their own institutions or reported limited reviews, [14–16] little is known regarding this topic.

In the present study, we elucidated several novel findings. First, we specified frequently encountered cancer types among patients in phase I trials and demonstrated their proportional changes over time. The distribution of frequently encountered cancer types in phase I trials differed considerably from that of estimated new cancer cases and that of estimated cancer deaths because cancer prognosis and treatment options vary with each type of cancer [17–19]. Second, patients with the two phase I major cancers, colorectal and lung cancer, were less likely to participate in phase I trials. The number of trials composed of a majority of patients with these two cancers also decreased. Third, patients with phase I uncommon cancers had come to account for a growing proportion of phase I trial patients. By enrolling patients with various types of cancer, the degree of efficacy on a broad spectrum could be evaluated. Fourth, the distributions of cancer types were relatively similar in North America and Europe, but differed in Asia. For

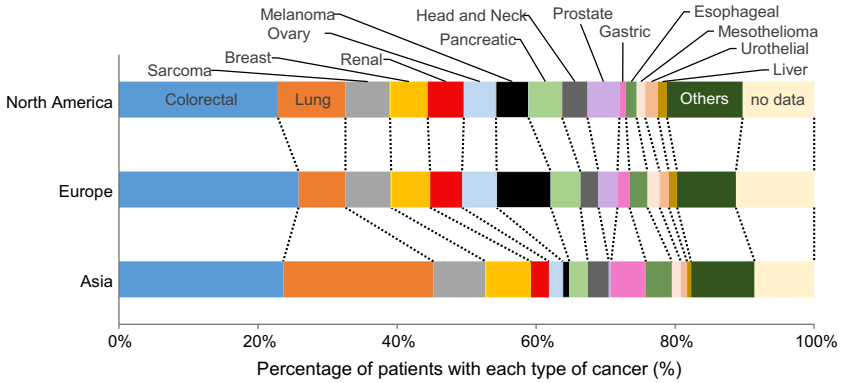


Fig. 4 Differences in Cancer Types Among Patients Between North America, Europe, and Asia in the Past 10 Years. The x-axis represents the proportion of patients with each type of cancer

some types of cancer, global trials or trials conducted in specific regions could be better strategies. These regional differences may be explained by differences in the incidence and mortality rates of each type of cancer and cancer treatment. The physician's specialty and the role of the institution in which phase I trials are conducted could also influence patient characteristics between trials and different regions.

From the 1990s through to the early 2000s, colorectal and lung cancer patients had played a pivotal role in numerous phase I trials. By the original nature of phase I trials, this remarkable imbalance in patient enrollment could be considered acceptable. This imbalance has gradually improved over time, leading to a diversification in the types of cancer observed among patients enrolled in phase I trials. One of the most probable reasons for the decline in the proportion of colorectal and lung cancer patients is that the treatments for some common types of cancer have seen greater advances and more standard lines of chemotherapy have been established. Following many lines of standard chemotherapy, the general condition and main organ function of patients tends to deteriorate, and thus, only a few patients are able to enter phase I trials. In addition, numerous antineoplastic agents have been approved for these cancers and patients can receive other approved drugs after standard chemotherapies instead of entering phase I trials. Although the decline in the incidence and mortality rates of patients with colorectal or lung cancer over time may be another reason, the percentage of estimated new cases and estimated deaths due to these two cancers have remained almost unchanged in America between 1995, 2005, and 2015 [17–19].

There has been intense discussion regarding the therapeutic benefit of phase I trials and early access to phase I trials remains controversial. The American Society of Clinical Oncology policy statement [20] insisted that clinicians present the option of participating in a clinical trial at each stage of cancer treatment, including phase I trials, before all other treatment options have failed. Phase I trials are expected to yield a response rate of approximately 5.0% and clinicians often hesitate to recommend phase I trials when standard treatment and other approved drug options remain available. However, the patient's needs, values, and preferences should also be considered when determining treatment. Participation in phase I trials could give patients great relief and improve their quality of life when appropriate patient selection is conducted [20, 21]. In this era of targeted therapies and immunotherapies, recent advances in cancer treatment could generate promising treatment options even in early clinical trial settings [8, 22].

Our study has several limitations. First, there was selection bias because we excluded trials that were likely to have enrolled a specific patient population. For example, immunotherapy trials were excluded because approximately 50% of the enrolled patients had renal cancer or melanoma. To minimize selection bias, prudent and rigorous article selection was performed by three investigators. Second, we could not acquire detailed information of cancer types from published articles. The cancer type was unknown in 11.6% of patients and this percentage remained consistent from 1991 to 2015.

Conclusions

We report on global trends in cancer types among patients enrolled in all-comer phase I trials. Diversification of enrolled patients in phase I trials is favorable in terms of increasing the likelihood of assessing the preliminary antitumor efficacy of new treatments against various types of cancer, especially rare cancers with unmet medical needs. However, the appropriate time to propose a phase I trial to each patient with a common type of cancer should be carefully considered to ensure that they do not lose the opportunity to receive investigational drugs. The distribution and regional differences in patient cancer types that we reported should be taken into consideration when establishing phase I trials with flexible and feasible designs and efficiently recruiting candidates to optimal phase I trials on a global scale.

Author contributions Itahashi and Yamamoto had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Itahashi, Yamamoto.

Acquisition, analysis, or interpretation of data: all authors.
Drafting of the manuscript: Itahashi, Shimizu, Yamamoto.
Critical revision of the manuscript for important intellectual content: all authors.
Statistical analysis: Itahashi.
Administrative, technical, or material support: Koyama, Yamamoto.
Study Supervision: Yamamoto.

Compliance with ethical standards

Conflict of interest disclosures Kota Itahashi has no conflicts of interest.

Toshio Shimizu has provided consulting for Takeda Oncology; received honoraria from Ono Pharmaceutical, ONO Pharma Taiwan CO., LTD., Boehringer Ingelheim, Taiho Pharmaceutical and Chugai Pharmaceutical; and received research funding from Takeda Oncology, PharmaMar, Bristol-Myers Squibb Japan, Daiichi Sankyo, SymBio Pharmaceuticals, Five Prime Therapeutics, and 3D Medicine.

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Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

Meeting presentation We presented this work at the Annual Meeting of the American Society of Clinical Oncology; June 2–6, 2017; Chicago, Illinois.

Disclaimer All opinions expressed by the authors in this paper are solely the author's opinions and do not reflect the opinions of the journal.

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