Clinical development of anticancer drugs can be enhanced using efficacy data of small population clinical trials

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Abstract
What Is Known and Objective: Although there are accelerated approval pathways based on data of small populations and surrogate endpoints, the concern that these pathways authorize the use of inefficacious drugs based on limited data from earlier phase clinical trials remains. We retrospectively investigated the efficacy of anticancer drugs, which were approved or whose development was terminated in small and large clinical trials, and verified whether small clinical trials could reflect the results for efficacy in large clinical trials.

Methods: All anticancer drugs approved in Japan or whose development was terminated from 2015 to 2019 were searched. The median overall survival (OS), median progression-free survival (PFS), and overall response rates (ORR) between small clinical trials (sample size ≤100) and large clinical trials (sample size >100) with identical target populations and treatment settings were compared. Simple linear regression analysis, Spearman's correlation analysis, and paired sample t-test were performed.

Results and Discussion: A total of 61 comparable small and large clinical trials were identified. For all endpoints, statistically significant linear trends and correlation were detected (p < 0.001). There were no statistically significant differences in the median PFS and ORR between small and large clinical trials. The mean differences of both clinical trials were −0.102 months and −1.531%, respectively.

What is new and Conclusion: Even when the sample size of the clinical trial was increased, the efficacy data of anticancer drugs could not be changed significantly. These results supported the accelerated approval pathway based on the promising efficacy data of small populations in anticancer drug development.

KEYWORDS accelerated approval, anticancer drug, efficacy, phase I clinical trial

1 | WHAT IS KNOWN AND OBJECTIVE

There are guidelines providing several pathways for the expedition of novel drug development and marketing authorization approval for unmet medical needs in the United States (US), Japan, and the European Union; moreover, a waiver may be granted to conduct confirmatory clinical trials under specific conditions.1 Many anticancer drugs have been approved based on the data of small populations and surrogate endpoints without the data of confirmatory clinical trials by following an accelerated approval pathway; moreover, withdrawals of accelerated approvals based on the results of post-approval confirmatory trials are limited.2–4 It was stated that the regulatory authority
had successfully applied accelerated approval pathways in oncology over the past three decades.³

However, it is still controversial to approve marketing authorization without a confirmatory clinical trial. Specifically, there is a risk that small, early phase clinical trials do not accurately reflect the efficacy data of large, randomized clinical trials because the small sample size in early phase clinical trials does not account for differences in patient characteristics.⁶ It is believed that the data of small populations and early phase clinical trials are insufficient to appropriately assess the efficacy profile of compounds; thus, this may lead to the approval of the use of inefficacious drugs.⁷ Validity of efficacy data in early clinical trials such as non-randomized, single-arm trials with limited sample sizes have not been investigated in detail.

Although there is continuous progress in technology and many anticancer drugs have been developed, there continues to be a high unmet need of novel curative treatment options in the field of oncology.⁸,⁹ Currently, many phase III clinical trials are being conducted for anticancer drug development, and large confirmatory clinical trials are time-consuming and costly. For example, it took approximately 4 years for drugs with accelerated approval to complete post-approval confirmatory clinical trials and convert their accelerated approval to regular approval.³ Moreover, the estimated median cost of a pivotal clinical trial is $19.0 million, and trials with a control arm are much more expensive than those without.¹⁰ In addition to the challenges mentioned above, there is also the ethical consideration of confirmatory trials with patients being already aware of the products undergoing investigation as being more efficacious and less toxic than the standard of care (e.g., chemotherapy); furthermore, they may be enrolled in the standard-of-care arm of the clinical trial, despite their wishes to receive the drug under investigation.¹¹ Therefore, it is expected that the accelerated approval pathway will be further implemented, considering the problems of the confirmatory trials above.

This investigation compares the efficacy data of small and large clinical trials and confirms whether small clinical trials that reflect the efficacy data of large clinical trials in anticancer drugs are assessed. Previous reports have compared the efficacy data of phase II and phase III clinical trials in anticancer drugs to confirm whether they provided comparable results.¹²,¹³ However, several anticancer drugs have recently been approved based on more limited data from earlier phase clinical trials (e.g., only phase I) with limited sample size.¹⁴ Thus, investigations comparing efficacy data between only phase II and phase III clinical trials cannot completely address the concerns of efficacy assessment regarding the accelerated approval of anticancer drugs. Therefore, further retrospective investigations are warranted to confirm whether smaller clinical trials (including phase I and phase I/II) of anticancer drugs showed different efficacy data of large clinical trials. This investigation includes the data of cases with failed development, which potentially affected the comparison of efficacy data between trials and were not considered in the previous reports above. This investigation will provide insights regarding the validity of accelerated approval pathways based on the limited efficacy data of small populations and early phase clinical trials.

2 | METHODS

2.1 | Clinical trial selection

In this investigation, the efficacy data of small and large clinical trials with comparable study design settings were extracted and compared. We constructed two databases of compounds approved as anticancer drugs and those unapproved but expected to be useful as anticancer drugs. The anticancer drugs approved in Japan from 2015 to 2019, including those with new therapeutic agent approval and those with supplemental approval (already approved for other indications, other dose levels, or other regimens), were extracted from the website of the Pharmaceuticals and Medical Devices Agency (PMDA). We defined clinical trials in which the sample size of the investigative product arm was ≤100 as a small clinical trial because the median sample size of the clinical trials that supported accelerated approval was approximately 100,²,⁹,¹⁵ whereas large clinical trials had a sample size >100. Small and large clinical trials that enrolled a population with approved indications and met the pairing criteria below were searched in the common technical document (CTD) registered on the PMDA’s website and published articles.

2.2 | Pairing criteria

- Enrolled identical tumour type
- Identical gene mutation or antigen expression when required for clinical trial participation
- Identical treatment line setting
- Identical dose level and regimen of the investigated product
- Identical dose level and regimen of combined treatment in case of a combined clinical trial

Unapproved compounds were also within the scope of this investigation and were noted as ‘development failure cases’. Unapproved compounds were identified from the repository of phase III clinical trials on ClinicalTrials.gov that enrolled cancer patients and was funded by the industry. The search terms used were ‘cancer’, status: ‘terminated’, completion date: ‘from 2015 to 2019’, study type: ‘interventional’, and study phase: ‘phase III’. Paediatric phase III clinical trials were outside the scope of this study. After the development failure cases were identified, we constructed a dataset of small and large clinical trials that met the pairing criteria. We also confirmed that none of the compounds from the development failure cases had been approved in Japan.

2.3 | Data collection

We analysed the median overall survival (OS), median progression-free survival (PFS), and overall response rate (ORR), which are key efficacy endpoints in almost all clinical trials of anticancer drugs. These data of the approved anticancer drugs in Japan were extracted
from the CTD registered on the PMDA’s website or published articles. The data of development failure cases were extracted from the ClinicalTrials.gov repository and other published articles. The median PFS and ORR data of clinical trials utilizing different assessment criteria or different versions of the assessment criteria were excluded from the analysis. Moreover, clinical trials in which the median OS and median PFS were not obtained were also excluded from the analysis. When there were multiple small or large clinical trials of the same compound that met the pairing criteria, all pairs were included in our analysis. For example, if two small clinical trials and one large clinical trial met the pairing criteria, two pairs of the small clinical trials and the large clinical trial would be analysed.

2.4 Data analysis

Simple linear regression analysis was performed to assess the relationship between the efficacy data of small and large clinical trials, as well as the predictability of efficacy data in large clinical trials based on that of small clinical trials. Spearman’s rank correlation analysis was performed to assess the correlation of the data of each efficacy endpoint between large and small clinical trials. Furthermore, the paired sample t-test was performed to determine whether there were statistically significant differences in the efficacy data between small and large clinical trials. All statistical analyses were performed using EZR software version 1.54 with \( \alpha = 0.05 \) as the threshold of statistical significance.

3 RESULTS AND DISCUSSION

A total of 142 drugs were approved in Japan, and 128 phase III clinical trials were terminated from 2015 to 2019. From these trials, 61 pairs of small and large clinical trials that met the pairing criteria were identified. Forty-seven pairs comprised approved anticancer drugs, and 14 pairs consisted of development failure cases. Additionally, the median OS, PFS, and ORR were obtained from 24, 26 and 49 pairs, respectively. The characteristics of the analysed pairs are listed in Table 1. The median sample sizes of the small and large clinical trials were 36 and 240, respectively, and approximately half of the small clinical trials were either phase I or I/II.

The mean and standard deviation of the median OS, median PFS and ORR in small and large clinical trials are shown in Table 1, and similar efficacy data were observed in small and large clinical trials. Scatterplots of the median OS, median PFS and ORR in small and large clinical trials are shown in Figure 1.

The results of the simple linear regression analysis, Spearman’s rank correlation analysis, and the paired sample t-test are shown in Table 2. A significant linear trend and correlation in the median OS, median PFS, and ORR between small and large clinical trials were observed. The correlation analysis showed that the correlation coefficients between both clinical trials were high for all endpoints, and the correlation coefficients of the median OS and ORR were >0.85, which was the threshold used to assess the validation of surrogate endpoints.\(^{17} \) The paired sample t-test showed there was a statistically significant difference of median OS between small and large clinical trials (\( p = 0.02 \)). In contrast, there were no statistically significant differences in the median PFS and ORR between small and large clinical trials, and the mean differences of the median PFS and ORR were \( -0.102 \) months and \( -1.531\% \), respectively. Additionally, it is worth noting that even when the sample size of the small clinical trial is limited (approximately 30–50), there were no significant differences in the median PFS and ORR. The endpoint used in clinical trials on the basis for granting accelerated approvals was mainly response rate.\(^{3} \) Therefore, this finding supports the use of the accelerated approval pathway, which is based on promising response rate data obtained from small populations in the early phase. These data suggest that pharmaceutical companies can confidently rely on the efficacy data of small clinical trials and should not expect more efficacious data in future large clinical trials.

It has been reported that phase III trials of several specific compounds failed despite predecessor trials that showed promising results.\(^{18,19} \) However, significant differences in the median OS, PFS, and ORR between comparable phase II and III clinical trials of anticancer drugs listed by the US Food and Drug Administration (FDA) were not observed, and their phase III trials failed to show the significant benefit of the investigated products, compared with comparators. In the report from Lara and Redman,\(^{19} \) there was a discrepancy in the concomitant medication setting, which potentially affected the efficacy data of phase II and III clinical trials. Beaver et al. reported that there were 10 accelerated approvals of confirmatory trials that did not end up showing clinical benefit; these are referred to as ‘dangling accelerated approvals’.\(^{5} \) Nine confirmatory trials of 10 dangling accelerated approvals with different patient populations and/or treatment settings, which potentially affected efficacy data from the previous trials supported accelerated approval. One confirmatory trial had the same patient population and treatment setting. However, significant differences were not observed in the median OS, PFS and ORR between the confirmatory trial and the previous trial that supported accelerated approval. In our investigation, we evaluated clinical trials with a more comparable study design, including the combinatorial treatment setting, which potentially impacts the efficacy data based on pairing criteria. This could have caused the varying results obtained in our investigation.

Furthermore, Vreman et al.\(^{12} \) studied the efficacy data between phase II and III clinical trials of anticancer drugs and reported no consistent differences in the median OS, PFS and ORR data, which was similar to the outcome of our investigation. However, while their investigation included only phase II and III clinical trials, our investigation included earlier phase clinical trials, including phase I and I/II. Therefore, the mean sample size of the small clinical trials in our analysis was 40.1, which was smaller than that of the investigation by Vreman et al.\(^{12} \) Nevertheless, a correlation between small and large clinical trials was observed, and statistically significant differences in the median PFS and ORR were not observed. Moreover, Vreman et al. reported only on compounds that were submitted to
|                              | Total (N [%]) | Median overall survival (N [%]) | Median progression-free survival (N [%]) | Overall response rate (N [%]) |
|------------------------------|---------------|---------------------------------|------------------------------------------|------------------------------|
| Total                        | 61            | 24                              | 26                                       | 49                           |
| Approved anticancer drug     | 47 (77.0)     | 12 (50.0)                       | 16 (61.5)                                | 41 (83.7)                    |
| Development failure cases    | 14 (23.0)     | 12 (50.0)                       | 10 (38.5)                                | 8 (16.3)                     |
| Tumour type                  |               |                                 |                                          |                              |
| Hematologic malignancy       | 25 (41.0)     | 2 (8.3)                         | 4 (15.4)                                 | 23 (46.9)                    |
| Solid malignancy             | 36 (59.0)     | 22 (91.7)                       | 22 (84.6)                                | 26 (53.1)                    |
| Line of treatment            |               |                                 |                                          |                              |
| 1st line                     | 17 (27.9)     | 5 (20.8)                        | 3 (11.5)                                 | 13 (26.5)                    |
| Later line                   | 44 (72.1)     | 19 (79.2)                       | 23 (88.5)                                | 36 (73.5)                    |
| Treatment                    |               |                                 |                                          |                              |
| Monotherapy                  | 25 (41.0)     | 15 (62.5)                       | 13 (50.0)                                | 18 (36.7)                    |
| Combinatory therapy          | 36 (59.0)     | 9 (37.5)                        | 13 (50.0)                                | 32 (62.3)                    |
| Median sample size (interquartile range) [range] |               |                                 |                                          |                              |
| Small clinical trial         | 36 (16.0–61.0) | 53 (35.0–64.0) [21–100]         | 51 (36.0–62.5) [6–100]                   | 31 (8.0–54.0) [6–100]       |
| Large clinical trial         | 240 (194.0–346.0) [109–682] | 237 (184–337.8) [111–682]      | 220 (187.0–333.0) [109–682]             | 240 (195.0–351.0) [109–682] |
| Randomized clinical trial    |               |                                 |                                          |                              |
| Small clinical trial         | 14 (23.0)     | 13 (54.2)                       | 11 (42.3)                                | 8 (16.3)                     |
| Large clinical trial         | 52 (85.2)     | 19 (79.2)                       | 19 (73.1)                                | 44 (89.8)                    |
| Phase                        |               |                                 |                                          |                              |
| Small clinical trial         |               |                                 |                                          |                              |
| I                            | 15 (24.6)     | 2 (8.3)                         | 2 (7.7)                                  | 14 (28.6)                    |
| I/II                         | 15 (24.6)     | 3 (12.5)                        | 8 (30.8)                                 | 13 (26.5)                    |
| II                           | 25 (41.0)     | 13 (54.2)                       | 10 (38.5)                                | 19 (38.8)                    |
| II/III                       | 1 (1.6)       | 1 (4.2)                         | 1 (3.8)                                  | 0 (0)                        |
| III                          | 5 (8.2)       | 5 (20.8)                        | 5 (19.2)                                 | 3 (6.1)                      |
| Large clinical trial         |               |                                 |                                          |                              |
| I                            | 0 (0)         | 0 (0)                           | 0 (0)                                    | 0 (0)                        |
| I/II                         | 6 (9.8)       | 3 (12.5)                        | 5 (19.2)                                 | 3 (6.1)                      |
| II                           | 5 (8.2)       | 2 (8.3)                         | 3 (11.5)                                 | 4 (8.2)                      |
| II/III                       | 3 (4.9)       | 3 (12.5)                        | 2 (7.7)                                  | 1 (2.0)                      |
| III                          | 47 (77.0)     | 16 (66.7)                       | 16 (61.5)                                | 41 (83.7)                    |
| Region                       |               |                                 |                                          |                              |
| Small clinical trial         |               |                                 |                                          |                              |
| Single region                | 37 (60.7)     | 8 (33.3)                        | 11 (42.3)                                | 34 (69.4)                    |
| Multiple region              | 23 (37.7)     | 15 (62.5)                       | 14 (53.8)                                | 14 (28.6)                    |
| Unknown                      | 1 (1.6)       | 1 (4.2)                         | 1 (3.8)                                  | 1 (2.0)                      |
| Large clinical trial         |               |                                 |                                          |                              |
| Single region                | 1 (1.6)       | 0 (0)                           | 0 (0)                                    | 1 (2.0)                      |
| Multiple region              | 60 (98.4)     | 24 (100)                        | 27 (100)                                 | 48 (98.0)                    |
| Mean of each efficacy endpoint (Standard deviation) [range] |               |                                 |                                          |                              |
| Small clinical trial         | 17.3 months (9.6) [3.6–51.4] | 7.7 months (6.4) [1.6–35.7]   | 54.0% (27.6) [0–100]                     |
| Large clinical trial         | 14.1 months (6.2) [3.0–32.5] | 7.6 months (6.7) [1.4–35.7]   | 52.4% (26.1) [3.7–92.9]                  |
the European Medicines Agency for approval and may have therefore been biased. The efficacy data of these phase III clinical trials tended to reflect that of phase II clinical trials or produce more efficacious data. In our investigation, the efficacy data of development failure cases were included. Additionally, in a study by Zia et al.\textsuperscript{13} a 12.9\% higher ORR was observed in phase II rather than phase III clinical trials.
trials. Meanwhile, our study demonstrated an approximately 1.6% higher ORR in small clinical trials than in large clinical trials. One possible reason for this discrepancy is that we included only eight pairs of clinical trials of development failure cases in the ORR dataset, and Zia et al. could have included more compounds whose development was terminated due to the unexpected and ineffectual results observed in phase III clinical trials, compared to those in phase II clinical trials. Another possible cause for the discrepancy is that we chose a more homogeneous patient population. Approximately 27% (13 pairs) of small and large clinical trials included in the ORR dataset enrolled cancer patients with specific antigen or gene mutation expression. Meanwhile, Zia et al. searched for clinical trials investigating chemotherapeutic regimens from 1998 to 2003, and it is the possible that these clinical trials investigated less specific and broader patient populations regardless of specific antigen or gene mutation expression. Therefore, it is possible that they compared the efficacy data of clinical trials that enrolled a more heterogeneous patient population with more inter-clinical trial variability and differences in patient characteristics. This could result in an efficacy gap between phase II and phase III clinical trials.

It is well-known that large clinical trials comparing the investigative product with the standard-of-care or placebo provide insights into the efficacy and safety of the new treatment option based on the high amount of patient data. However, anticancer drug development is active and fast, with a rapidly evolving standard-of-care. Therefore, there is an increasing need for faster development of anticancer drugs; thus, conducting time-consuming, large, randomized phase III clinical trials is no longer ideal for anticancer drug development because it is possible that the standard-of-care will change before a large clinical trial can be completed, thereby making its findings obsolete. As mentioned above, there is an ethical challenge regarding patient enrollment in the comparator arm of randomized, confirmatory clinical trials. In our study, more than 85% of large clinical trials were randomized, and a total of 9150 patients were enrolled in the comparator arm of a placebo-controlled or actively-controlled trial. Moreover, our database included 27 large clinical trials that targeted patients who received previous treatment and experienced disease progression. Therefore, it is expected that many patients were hoping to receive new treatment and thus participated in the clinical trials; however, they were enrolled in the standard-of-care or placebo arm of the previous clinical trial. In addition, phase III confirmatory trials are costly, and a placebo-controlled clinical trial is even more expensive than studies without a control group. Thus, a limited research and development budget provides a challenge to the future development of health technology. We believe that the accelerated approval pathway can help eliminate the challenges of large clinical trials by granting patients earlier access to novel drugs and reducing ethical dilemmas, time, and cost of confirmatory clinical trials. It is important to add that the evaluation of whether accelerated approval should be converted to regular approval or withdrawn must be conducted on a timely basis once the post-approval confirmatory trial is completed.

Finally, we extracted the data of compounds whose clinical trials in ClinicalTrials.gov were terminated as development failure cases. However, there were also compounds in phase III clinical trials registered as “completed” whose development was stopped or paused by the pharmaceutical company due to unexpected efficacy and safety results in clinical trials. These cases were not evaluated in our datasets as development failure cases.

4 | WHAT IS NEW AND CONCLUSION

To summarize, our research suggested that there were no significant differences in median PFS and ORR between small and large clinical trials, and even when the sample size of the clinical trial was increased, efficacy data of the anticancer drug would not be changed significantly. These results support the application of the accelerated approval pathway based on the promising data of a small population and early phase clinical trials in drug development targeting life-threatening cancers with a high unmet need of novel curative treatment options.

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CONFLICT OF INTEREST

Keiichi Sawachi is an employee of Astellas Pharma Inc.; however, this has not influenced the results and discussion presented in this paper. All remaining authors have declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this investigation are included in the published articles, CTD registered on the PMDAs website, and ClinicalTrials.gov repository.

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