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ORIGINAL ARTICLE

Early phase clinical trial played a critical role in the Food and Drug Administration−approved indications for targeted anticancer drugs: a cross-sectional study from 2012 to 2021

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Abstract

Objectives: To characterize the indications approved by the US Food and Drug Administration (FDA) on the basis of early phase clinical trials (EPCTs) and compared with that of phase three randomized controlled trials.

Study Design and Setting: We collected the publicly available FDA documents of targeted anticancer drugs approved between January 2012 and December 2021.

Results: We identified 95 targeted anticancer drugs with 188 indications approved by the FDA. One hundred and twelve (59.6%) indications were approved on the basis of EPCTs, with a significant increase of 22.2% per year. Of 112 EPCTs, 32 (28.6%) were dose-expansion cohort trials and 75 (67.0%) were single-arm phase 2 trials, respectively, with a significant increase of 29.7% and 18.7% per year. Compared with indications approved on the basis of phase three randomized controlled trials, the indications approved on the basis of EPCTs had significantly higher odds in receiving accelerated approval and lower odds in the number of entered patients of pivotal trials.

Conclusions: Dose-expansion cohort trials and single-arm phase 2 trials played a critical role in EPCTs. EPCT was a major trial type in providing evidences for the FDA approvals of targeted anticancer drugs.

Keywords: Early phase clinical trial; Dose-expansion cohort; Single-arm trial; Pivotal trial; FDA approved indications; Targeted anticancer drugs

1. Introduction

With the development of precision oncology, molecular targeted anticancer drug has become the most attractive research field in new drug development [1]. A lot of time, money and resources have been invested in developing novel targeted anticancer drugs [2]. More and more blockbuster drugs have been approved by the US Food and Drug Administration (FDA) in the past decades [3]. However, historical data showed that only less than 10% of new drug applications (NDAs) could get approvals from the FDA [4,5]. Most of NDAs failed in providing sufficient efficacy and safety data in clinical trials and thus solid

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What is new?

Key findings

- One hundred and twelve (59.6%) indications were approved by the FDA on the basis of EPCTs, with a significant increase of 22.2% per year between 2012 and 2021.
- EPCT mainly included two types of clinical trials: dose-expansion cohort (DEC) and single-arm phase 2 trials (Phase 2 SATs). Out of 112 EPCTs, 32 (28.6%) were DEC trials and 75 (67.0%) were Phase 2 SATs, respectively, with a significant increase of 29.7% and 18.7% per year.
- Compared with phase 3 RCTs, EPCTs had significantly higher odds in receiving accelerated approval and lower odds in the number of entered patients of pivotal trials.

What this adds to what is known?

- The study provided a new landscape of EPCTs in clinical development of targeted anti-cancer drug.

What is the implication and what should change now?

- This study provided a historical reference in valuation and application of EPCT strategies during targeted anti-cancer drug clinical development for investigators and relative researchers.

evidence from pivotal clinical trial is the key point in the application of drug approvals [4,6].

During the improvement of highly selective targeted therapies, the landscape of pivotal clinical trial evidences has changed substantially, especially the early phase clinical trial (EPCT) that was used as pivotal trial evidence in the NDAs to the FDA [7,8]. Dose-expansion cohort (DEC) trial is one of the most frequently used types of EPCT in the supporting of NDAs [9]. In addition to phase 1a trial evidences in drug metabolism and dose-limiting toxicity, the DEC trials are also taken as phase 1b or phase I/II trials to provide evidences in preliminary efficacy and optimal disease-specific setting [9,10]. Recently, many of highly active targeted novel drugs were approved by the FDA on the basis of DEC trials, especially for advanced and refractory cancers to match the unmet clinical needs [7,9,11,12]. Another type of EPCT is single-arm phase 2 trial (Phase 2 SAT) that usually is used as a pivotal trial in the NDA [13,14]. Compared with randomized controlled trials (RCTs), phase 2 SATs only contain treatment groups, thus avoiding potential ethical issues of using placebo or inactive treatment for patients with serious conditions [8,14]. Moreover, the sample sizes in phase 2 SATs are usually smaller than that of phase three RCTs [8,15]. Drugs marketed on the basis of phase 1 or phase 2 trials have many advantages in saving time, resources, and enabling cancer patients to use new drugs as soon as possible [8,15]. Today, EPCT evidences are widely used in the application of novel targeted anticancer drugs to the FDA [7,9]. However, a comprehensive study is still lacking in the distribution and epidemiological characteristics of these EPCTs and their corresponding indications approved by the FDA.

In the past 10 years, we identified more than 180 indications with about 100 novel molecular targeted anticancer drugs received approvals from the FDA, relating to a significant improvement in the therapeutics of serious and life-threatening oncologic diseases. It is a milestone for targeted anticancer therapies. To investigate and summarize the trends and characteristics of these indications and their pivotal trial evidences are important for further new targeted drug development. In this study, the FDA data for molecular targeted anticancer drugs between 2012 and 2021 were collected to determine the proportion of indications approved on the basis of EPCTs and traditional phase three RCTs. We examined the trend in the number of approved indications and evaluated the association between indication characteristics and the use of EPCTs and phase three RCTs, providing a historical reference in targeted anticancer drug clinical development for investigators, sponsors, and contract research organization.

2. Materials and methods

2.1. Sample identification

The original and supplemental applications of targeted anticancer drug were listed by the FDA. The data were publicly available in the Drugs@FDA database [16]. In this study, we included all the FDA-approved indications of targeted anticancer drugs between 2012 and 2021. Only indications of single agent were included. We excluded the indications of adjuvant treatment or maintenance treatment. We also excluded the nontherapeutic indications such as diagnostic and contrast drug indications. Two investigators (Y.H. and J.Z.) extracted all the indication approvals from the FDA database and examined the FDA's letters that accompanying the approvals to identify whether the approval included a new indication. If the indication was related to two or more application approvals, for example, ''accelerated approval'' or ''labeling change with clinical data,'' these approvals were counted as one indication.

Each approved indication includes corresponding clinical trials that supported the indication. Pivotal trial is the basis of the approval. We considered a trial to be pivotal if the FDA medical review defined as such. If not specific,

the efficacy trials that served as the essential to the indication approvals were considered to be pivotal. We identified all the pivotal trials of each indication.

2.2. Data extraction

Two investigators (Y.H. and J.Z.) extracted the key information from the FDA databases of each application approval, including year of approval, approval pathway (accelerated, not accelerated), breakthrough therapy designation (yes, no), orphan drug designation (yes, no), review type (priority, standard), type of submission (original, supplemental), and drug type (small-molecular kinase inhibitors, antibodies or antibody-drug conjugates, others). For each approved indication, detailed information was also collected, including cancer type (solid cancer, hematological malignancies) and first-line treatment (yes, no). Each approved indication could include one or more pivotal trials in the supporting of the application. We identified these pivotal trials from the FDA's drug review dossiers and labeling. We extracted the information on the number of trials that supported the indication application by excluding the trials that serve as the postmarketing modifications. We also extracted the information on the number of entered patients and the uses of primary efficacy outcomes (overall survival, progression-free surviva, and tumor response rate).

If multiple pivotal trials supported only one indication, we then selected the one at the most advanced trial phase and examined the study design of the selected trial that supporting the application approval. An EPCT was defined as a trial at phase 1 or phase 2, without a comparative phase three RCT design [7]. An DEC trial was defined as a trial with an initial dose-escalation phase, followed by more than two cohorts with additional subject under the cohort-specific objectives [9]. A phase 2 SAT was defined as a nonrandomized phase 2 trial [8].

2.3. Statistical analysis

Descriptive statistics were used to characterize application approvals and indications. We evaluate the number of approved indications over time, respectively, using the indications that were approved on the basis of EPCTs, phase three RCTs, DEC trials, and phase 2 SATs. Poisson models were used, with the number of approved indications as dependent variable and with a linear term for year of approval. The trends were estimated as incidence rate ratios (IRRs) with 95% confidence intervals (CIs).

Associations between indication and trial characteristics were estimated as odds ratios (ORs) with 95% CIs using logistic regression with univariable models and multivariable models, respectively. In the multivariable model 1, we adjusted for type of submission (original, supplemental). In the multivariable model 2, to control potential confounding from type of approval, we additionally adjusted for approval pathway (accelerated, not accelerated). The comparison was conducted between the indications that were approved on the basis of, respectively, EPCTs and phase three RCTs, DEC trials and phase three RCTs, phase 2 SATs and phase three RCTs, and DEC trials and phase 2 SATs. A two-sided alpha was used and a P value less than 0.05 was considered significant. All the analyses were performed using SAS, version 9.4 (SAS Institute, Cary, North Carolina).

3. Results

3.1. Characteristics and trends in the number of approved indications of targeted cancer drugs between 2012 and 2021

A total of 188 indications were approved by the FDA between 2012 and 2021, which included 95 targeted anticancer drugs (Table A.1). There was a significant increase of 14.5% per year (IRR 1.145, 95% CI 1.087 to 1.207, $P < 0.001$) in the number of all approved indications in the past 10 years. Of 188 indications, 79 (42.0%) were approved based on small-molecular kinase inhibitors, 79 (42.0%) were approved based on antibodies or antibody-drug conjugates, and 30 (16.0%) were approved based on other drug types. One hundred and twenty nine of 188 (68.6%) indications were developed for solid cancer and 59 (31.4%) for hematological malignancies (Table 1).

One hundred and twelve (59.6%) indications were approved on the basis of EPCTs, with a significant increase of 22.2% per year (IRR 1.222, 95% CI 1.138 to 1.312, $P < 0.001$). Of the 112 EPCTs, 32 (28.6%) were DEC trials and 75 (67.0%) were phase 2 SATs, respectively, with a significant increase of 29.7% per year (IRR 1.297, 95% CI 1.126 to 1.493, $P < 0.001$) and 18.7% per year (IRR 1.187, 95% 1.091 to 1.292, $P < 0.001$). Seventy six (40.4%) indications were approved on the basis of phase three RCTs, with an increase of 5.0% per year (IRR 1.050, 95% 0.971 to 1.136, $P = 0.221$) (Figs. 1 and 2).

3.2. Comparison of characteristics between indications approved on the basis of EPCTs and phase three RCTs

Compared with indications on the basis of phase three RCTs, indications that were approved on the basis of EPCTs had significantly higher odds in the number of approvals from 2017 to 2021 (OR = 2.123; 95% CI, 1.071 to 4.207, $P = 0.031$) and in receiving accelerated approval (OR = 35.5; 95% CI, 13.122 to 96.039, $P < 0.001$). Indications that were approved on the basis of EPCTs had significantly lower odds in solid cancer (OR = 0.380; 95% CI, 0.192 to 0.750, $P = 0.005$), first-line treatment (OR = 0.336; 95% CI, 0.153 to 0.738, $P = 0.007$), and in the number of entered patients (OR = 0.983; 95% CI, 0.978 to 0.988, $P < 0.001$) (Table A.2). The direction

Table 1. Characteristics of indications and pivotal trials approved by the FDA for targeted anticancer therapy from 2012 to 2021

Characteristic	Indications supported on the basis of			
	Dose-expansion cohort trials (n = 32)	Single-arm phase 2 trials (n = 75)	Early phase clinical trials (n = 112)[a]	Phase three RCTs (n = 76)
Year of approval, No. (%)				
2012–2016	5 (15.6)	14 (18.7)	20 (17.9)	24 (31.6)
2017–2021	27 (84.4)	61 (81.3)	92 (82.1)	52 (68.4)
Approval pathway, No. (%)				
Accelerated	22 (68.8)	57 (76.0)	80 (71.4)	5 (6.6)
Not accelerated	10 (31.3)	18 (24.0)	32 (28.6)	71 (93.4)
Breakthrough therapy designation, No. (%)				
Yes	20 (62.5)	33 (44.0)	55 (49.1)	17 (22.4)
No	12 (37.5)	42 (56.0)	57 (50.9)	59 (77.6)
Orphan drug designation, No. (%)				
Yes	22 (68.8)	52 (69.3)	75 (67.0)	38 (50.0)
No	10 (31.3)	23 (30.7)	37 (33.0)	38 (50.0)
Review type, No. (%)				
Priority	27 (84.4)	46 (61.3)	77 (68.8)	39 (51.3)
Standard	5 (15.6)	29 (38.7)	35 (31.3)	37 (48.7)
Type of submission, No. (%)				
Initial	22 (68.8)	39 (52.0)	63 (56.3)	27 (35.5)
Supplemental	10 (31.3)	36 (48.0)	49 (43.8)	49 (64.5)
Drug type, No. (%)				
Small-molecular kinase inhibitors	18 (56.3)	26 (34.7)	47 (42.0)	32 (42.1)
Antibodies or ADCs	9 (28.1)	38 (50.7)	48 (42.9)	31 (40.8)
Others[b]	5 (15.6)	11 (14.7)	17 (15.2)	13 (17.1)
Cancer type, No. (%)				
Solid cancer	23 (71.9)	42 (56.0)	68 (60.7)	61 (80.3)
Hematological malignancies	9 (28.1)	33 (44.0)	44 (39.3)	15 (19.7)
First-line treatment, No. (%)				
Yes	4 (12.5)	7 (9.3)	12 (10.7)	20 (26.3)
No	28 (87.5)	68 (90.7)	100 (89.3)	56 (73.7)
No. of trials supporting approval				
One trial	28 (87.5)	66 (88.0)	99 (88.4)	63 (82.9)
More than one trial	4 (12.5)	9 (12.0)	13 (11.6)	13 (17.1)
No. of entered patients, Median (IQR)	100 (54.5 to 158.5)	102 (69 to 134)	103 (64.5 to 142.5)	382 (297 to 711.5)
Use OS as primary outcome, No. (%)				
Yes	0 (0)	0 (0)	0 (0)	28 (36.8)
No	32 (100.0)	75 (100.0)	112 (100.0)	48 (63.2)
Use PFS as primary outcome, No. (%)				
Yes	0 (0)	2 (2.7)	2 (1.8)	47 (61.8)
No	32 (100.0)	73 (97.3)	110 (98.2)	29 (38.2)
Use RR as primary outcome, No. (%)				
Yes	31 (96.9)	73 (97.3)	109 (97.3)	8 (10.5)
No	1 (3.1)[c]	2 (2.7)	3 (2.7)	68 (89.5)

Abbreviations: ADCs, antibody-drug conjugates; IQR, interquartile range; OS, overall survival; PFS, progression-free survival; RCTs, randomized controlled trials; RR, tumor response rate.

[a] Including 75, 32, four, and one indications approved on the basis of, respectively, single-arm phase 2 trials, dose-expansion cohort trials, phase 2 randomized dose-comparison trials, and phase 2 randomized comparative trial.

[b] Others include aromatase inhibitor, histone deacetylase inhibitors, other enzyme inhibitors, and hormone drugs.

[c] Use tumor response rate as secondary outcome.

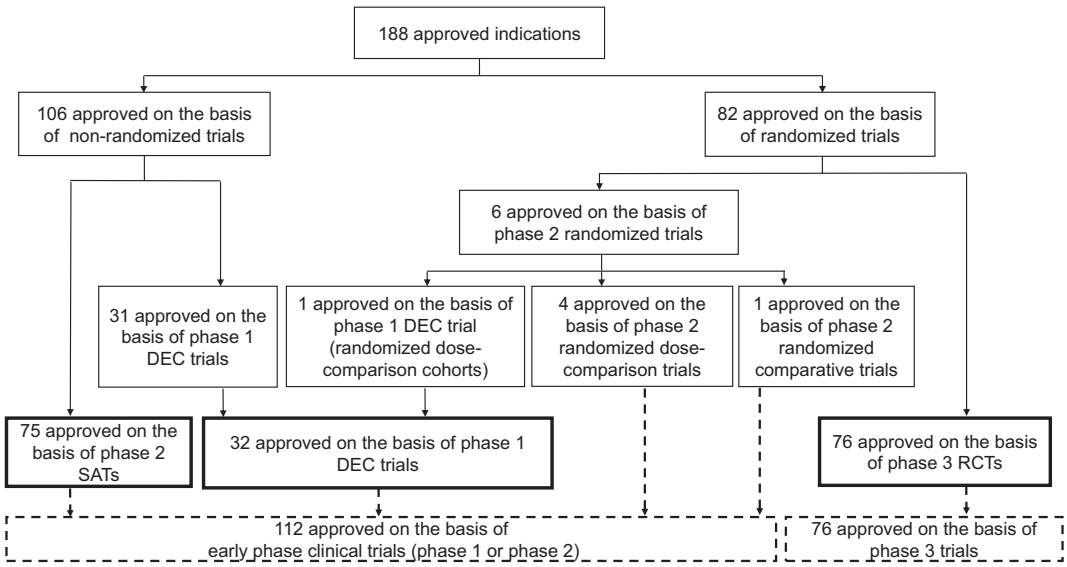

Fig. 1. Indications approved by the FDA for targeted anticancer therapy from 2012 to 2021. *Abbreviations:* DEC, dose-expansion cohort; RCT, randomized controlled trial; SAT, single-arm trial.

and statistical significance did not change after adjusting for type of submission and approval pathway (Table 2).

3.3. Comparison of characteristics between indications approved on the basis of DEC trials and phase three RCTs

Compared with indications on the basis of phase three RCTs, indications that were approved on basis of DEC trials had significantly higher odds in receiving accelerated approval (OR = 31.233; 95% CI, 9.643 to 101.157, $P < 0.001$). Indications that were approved on basis of DEC trials had significantly less number of entered patients (OR = 0.971; 95% CI, 0.957 to 0.984, $P < 0.001$) (Table A.3). After adjusting for type of submission and approval pathway, indications that were approved on the basis of EPCTs showed significantly higher odds in the number of approvals from 2017 to 2021 (OR = 6.315; 95% CI, 1.256 to 31.750, $P = 0.025$), as compared with indications on the basis of phase three RCTs (Table 2).

3.4. Comparison of characteristics between indications approved on the basis of phase 2 SATs and phase three RCTs

Compared with indications on the basis of phase three RCTs, indications that were approved on basis of phase 2 SATs had significantly higher odds in receiving accelerated approval (OR = 44.964; 95% CI, 15.730 to 128.531, $P < 0.001$) and had significantly less number of entered patients (OR = 0.984; 95% CI, 0.979 to 0.989, $P < 0.001$) (Table A.4). The direction and statistical significance did not change after adjusting for type of submission and approval pathway (Table 2).

3.5. Comparison of characteristics between indications approved on the basis of DEC trials and phase 2 SATs

Compared with indications on the basis of phase 2 SATs, indications that were approved on basis of DEC trials had higher odds in priority review (OR = 3.404; 95% CI, 1.178 to 9.839, $P = 0.024$). After adjusting for type of submission and approval pathway, the result became insignificant (OR = 2.914; 95% CI, 0.919 to 9.240, $P = 0.069$) (Table A.5).

4. Discussion

In this study, we provided a profile of 188 indications approved by the FDA between 2012 and 2021 for 95 molecular targeted anticancer drugs. We found that 59.6% of the indications were approved on the basis of EPCTs. There was a significant increase of 22.2% per year in the number of approvals on the basis of EPCTs, although the increase was only 5.0% per year for that of phase three RCTs in the past decade. EPCTs played an important role in providing preliminary efficacy and safety evidences in molecular-targeted anticancer therapy. The vigorous development of EPCT evidences in anticancer targeted therapies illustrated the precision oncology success in the strategy of shorten clinical research period by trial design improvement for the initial NDA of molecular targeted drugs [7,17]. Moreover, we found a significant less number of entered patients in EPCTs when compared with that in phase three RCTs. Previous study showed that most new drugs are traditionally marketed through phase three RCT within a clinical development cycle that typically consumes about 7 years [18]. Approvals on the basis of EPCT evidences could be helpful in saving time, money, and

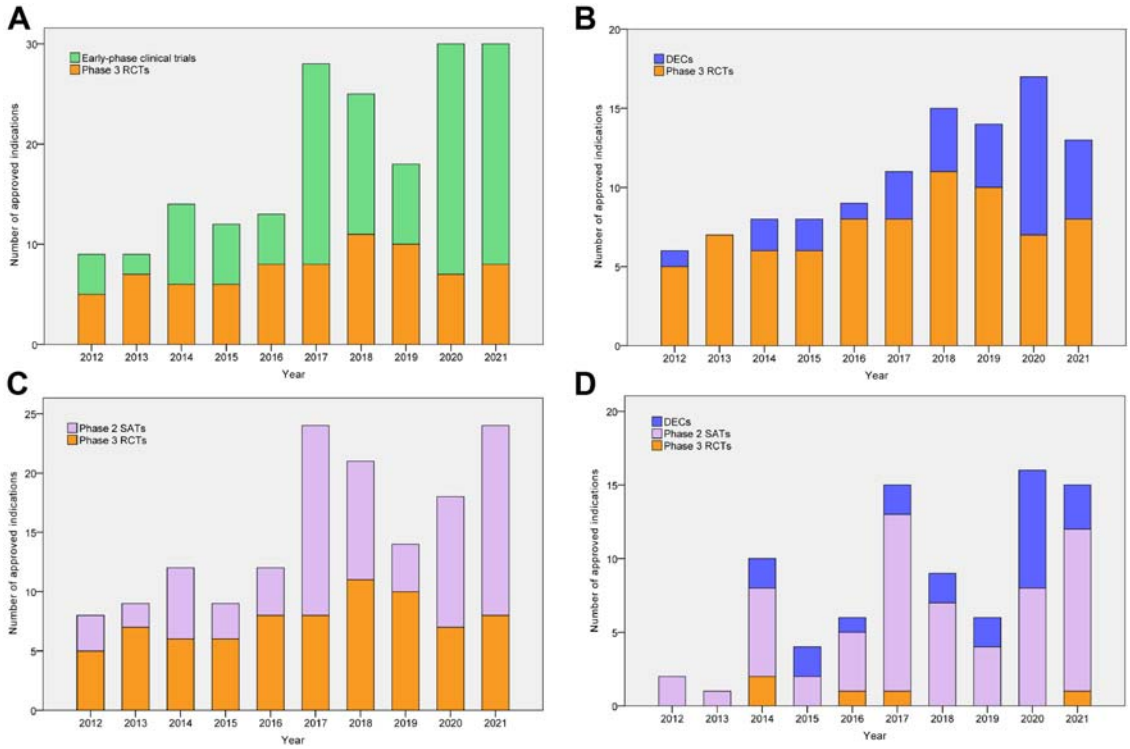

Fig. 2. Annual numbers of newly approved indications by types of pivotal trial. (A) Early phase clinical trials vs. phase three RCTs; (B) DECs vs. phase three RCTs; (C) phase 2 SATs vs. phase 3 RCTs; (D) the numbers of indications through accelerated approval pathway by types of pivotal trial. *Abbreviations:* DEC, dose-expansion cohort; RCT, randomized controlled trial; SAT, single-arm trial.

resources at the premarketing stage for drug development. Expediting the development of potentially important novel anticancer drugs would facilitate patients' access to novel drugs as early as possible. Nevertheless, efficacy demonstration in EPCT usually depends on surrogate outcomes or intermediate clinical end points and the clinical benefits such like overall survival would be confirmed in the postapproval studies [19−21].

Among the 112 indications approved on the basis of EPCTs, 32 (28.6%) indications were approved on the basis of DEC trials and had a significant increase of 29.7% per year, which was the highest when compared with that of other indications. Recently, DEC trial attracts the attention of many clinical investigators because of its compacted and relatively simple structure in trial design and its higher efficiency and easier conducting than that of RCTs [18]. In a DEC trial, the expansion cohorts and traditional phase I dose escalation are designed in a single clinical trial protocol [9]. In this protocol, the designed DEC seamlessly proceed from the determination of dose-limiting toxicity and recommended phase 2 dose to the estimation of antitumor activity and clinical efficacy, which are more traditionally estimated in phase 2 trials [9,22]. Typically, the DEC trial adds additional number of eligible patients to recommended phase 2 dose cohort in dose escalation. The number of cohorts is usually determined by a basket design of targeted cancer types and potentially specific patient subgroups. These DECs enable investigators to efficiently gain early evidence on whether a developed agent could be effective across the diseases and patients in the context of a single trial rather than using separate phase I trials and multiple phase II trials in specific patient populations [9,10,17]. To date, an increasing number of DEC trials is considered as pivotal trials that demonstrate the efficacy and safety and provide critical evidence for the approvals of targeted anticancer drugs [23−26]. In this study, we found that indications approved on the basis of DEC trials were more likely to receive accelerated approval, granting breakthrough designation, under priority review and with initial submission of the application. The number of entered patients was significantly smaller in DEC trials when compared with that in phase three RCTs. Although the DEC trial has showed its popularity in past decade, there are still many needs on its methodological design, for example, improvements on the sample size calculation method and standardization of results reporting [7,27−29].

This study found that among the indications approved on the basis of EPCTs, 75 (67.0%) of them were on the basis of phase 2 SATs. There was a significant increase of 18.7% per year from 2017 to 2021. Compared with indications approved on the basis of phase three RCTs, indications on the basis of phase 2 SATs were more likely to receive an accelerated approval. The number of entered patients was significantly lower in phase 2 SATs when compared with that of phase three RCTs. Most of indications of targeted anticancer drugs focus the treatment on unresectable

Table 2. Multivariable logistic regression models of covariables associated with the approvals of targeted anticancer drug from 2012 to 2021

Characteristic	EPCTs vs. phase 3 RCTs		DEC trials vs. phase 3 RCTs		Phase 2 SATs vs. phase 3 RCTs	
	Adjusted odds ratio (95% CI)[a]	*P* value	Adjusted odds ratio (95% CI)[a]	*P* value	Adjusted odds ratio (95% CI)[a]	*P* value
Year of approval						
2012–2016	1 (Reference)	—	1 (Reference)	—	1 (Reference)	—
2017–2021	3.312 (1.218–9.008)	0.019	6.315 (1.256–31.750)	0.025	2.973 (0.928–9.521)	0.067
Approval pathway						
Not accelerated	1 (Reference)	—	1 (Reference)	—	1 (Reference)	—
Accelerated	34.362 (12.615–93.599)	<0.001	30.848 (8.933–106.527)	<0.001	44.135 (15.345–126.944)	<0.001
Breakthrough therapy designation						
No	1 (Reference)	—	1 (Reference)	—	1 (Reference)	—
Yes	2.204 (0.957–5.079)	0.063	3.875 (1.168–12.851)	0.027	1.618 (0.599–4.371)	0.343
Orphan drug designation						
No	1 (Reference)	—	1 (Reference)	—	1 (Reference)	—
Yes	1.275 (0.584–2.787)	0.542	1.780 (0.551–5.751)	0.336	1.565 (0.617–3.970)	0.345
Review type						
Standard	1 (Reference)	—	1 (Reference)	—	1 (Reference)	—
Priority	2.208 (0.966–5.051)	0.061	5.792 (1.325–25.322)	0.020	1.444 (0.558–3.741)	0.449
Type of submission						
Supplemental	1 (Reference)	—	1 (Reference)	—	1 (Reference)	—
Initial	2.075 (0.96–4.485)	0.063	3.898 (1.219–12.466)	0.022	1.797 (0.722–4.476)	0.208
Drug type						
Small-molecular kinase inhibitors	0.811 (0.364–1.809)	0.609	0.894 (0.278–2.875)	0.850	0.580 (0.216–1.555)	0.279
Antibodies or ADCs	1.065 (0.463–2.446)	0.883	0.604 (0.169–2.156)	0.438	1.698 (0.628–4.590)	0.297
Others[b]	1.263 (0.470–3.394)	0.643	2.289 (0.569–9.205)	0.244	1.058 (0.314–3.568)	0.928
Cancer type						
Hematological malignancies	1 (Reference)	—	1 (Reference)	—	1 (Reference)	—
Solid cancer	0.298 (0.124–0.716)	0.007	0.333 (0.090–1.234)	0.100	0.426 (0.156–1.159)	0.095
First-line treatment						
No	1 (Reference)	—	1 (Reference)	—	1 (Reference)	—
Yes	0.328 (0.111–0.975)	0.045	0.447 (0.097–2.052)	0.300	0.261 (0.067–1.009)	0.052
No. of trials supporting approval						
One trial	1 (Reference)	—	1 (Reference)	—	1 (Reference)	—
More than one trial	0.555 (0.175–1.759)	0.318	0.421 (0.080–2.213)	0.307	0.639 (0.168–2.433)	0.512
No. of entered patients	0.983 (0.977–0.989)	<0.001	0.972 (0.956–0.988)	0.001	0.984 (0.978–0.991)	<0.001

Abbreviations: ADCs, antibody-drug conjugates; DEC, dose-expansion cohort; EPCTs, early phase clinical trials; RCTs, randomized controlled trials; RR, tumor response rate; Phase, 2 SATs, single-arm phase 2 trials.

[a] Adjusted for type of submission (original, supplemental) and approval pathway (accelerated, not accelerated).

[b] Others include aromatase inhibitor, histone deacetylase inhibitors, other enzyme inhibitors, and hormone drugs.

or metastatic cancer patients, who are usually in the serious and life-threatening condition. SATs are suitable for these patients because the patients have no optimal treatment as the positive control and cannot use placebo as negative controls for ethical problems [8]. RCTs may raise ethical issues as such. Phase 2 SATs use historical controls in the design to solve the ethical concerns. But it may also raise potential selection bias and confounding bias in SATs [8]. Phase 2 SATs are simpler and easier to conduct when compared with RCTs. Moreover, a smaller sample size than RCTs is normally required in phase 2 SATs. Nevertheless, RCTs are the gold standard to provide efficacy and safety evidences. It is still necessary to conduct RCTs in the real-world setting to confirm clinical benefits for the indications approved on the basis of SATs [30,31].

Our study shows a significant increasing use of EPCT in the FDA approval in the past decade. It is challenging our thinking of the classical paradigm of targeted anticancer

drug development, which comprises phase 1, phase 2, and phase three clinical trials. The following reasons may explain the increasing use of EPCT in NDAs these years. First, with the deep exploration and understanding of precision oncology, many molecular targets are found and used as biomarkers to divide cancer patients into subgroups. For example, nonsmall cell lung cancer (NSCLC) could be divided into at least seven subtypes by different types of cancer driver genes (CDGs) such like ALK, RET, and ROS1 [11]. Thus, the large number of NSCLC patients would be divided into many subtypes based on CDG-positive conditions. The number of patients in each subtype would be very small, which makes the CDG-positive NSCLC a rare cancer. The small number of cancer patients in the subtype could make it difficult to match the old phase 1, phase 2, and phase three study designs as before [32]. For example, RET-positive NSCLC patients only account for 1%−1.5% of NSCLC patients [33]. Selpercatinib and pralsetinib as RET inhibitors, respectively, obtained the FDA-accelerated approvals on the basis of DEC trials [33,34]. Second, the candidate drug showed dramatic effects. For example, immune-checkpoint inhibitors had dramatic treatment effects and many of them such as pembrolizumab in metastatic melanoma treatment achieved the FDA approvals on the basis of EPCT evidences [35−38]. Third, extensive statistical involvement in the EPCTs also contributes a lot. With the development of model-based designs such as the continual reassessment method and the Bayesian two-stage designs, using of these trial designs has become more prevalent in DEC trials and SATs [7,27,28,39]. Fourth, trial conduction was improved greatly. For example, the FDA issued the process standards of clinical trial imaging end point in 2018 for independent review committee in EPCTs and it made the surrogate end points more objective than investigator's decision did [40].

Nevertheless, it should be still noted that the evidence level of EPCTs is not as high as that of phase three RCTs. Further efforts are needed to reduce the potential risk of bias of EPCTs, including standardization of statistical analysis plans, optimization of the tools in assessing the risk of bias, and applicability of EPCTs [7,17,41−43]. Above all, this study provides a landscape of EPCT evidences in the FDA-approved indications of novel targeted anticancer drugs, suggesting that relative researchers to value and apply EPCT strategies during targeted anticancer drug development. With development of the US Precision Medicine Initiative launched in 2015, more and more attention to study the EPCT evidences from candidate-targeted drugs will be paid to accelerate progress toward a new era in precision oncology.

There were two limitations. First, the resources in this study were limited to those materials presented by the FDA and did not include information from other agencies. Although many of these agencies are regulatory members of The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, harmonization is achieved through guidelines via the scientific consensus [44]. It is very likely that similar findings could be produced from these agencies. Second, this cross-sectional study only included the indications approved in the past decade because it covered majority of targeted anticancer drugs [45,46].

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Supplementary data

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