Indications and pivotal trials of the FDA approved small-molecular kinase inhibitors in cancer therapies with and without biomarker of cancer driver gene

Yafang Huang (yafang@ccmu.edu.cn)
Capital Medical University
Weiyi Xiong
National Center for ADR monitoring
Li Ma
Capital Medical University
Hao Wu
Capital Medical University

Research Article

Keywords: Cancer driver gene, Small-molecular kinase inhibitors, FDA approval, Pivotal trial, Precision oncology

Posted Date: March 15th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1443724/v1

Abstract

Background: Cancer precision medicine with biomarker of cancer driver gene (CDG) has been achieved by many small-molecular kinase inhibitors (SMKIs) approved by the US Food and Drug Administration (FDA). We characterized their indications and pivotal trials with and without CDG biomarker.

Methods: Publicly available FDA documents were collected for all SMKI cancer drugs approved between January 2001 and December 2021. Characteristics of indication and pivotal trial were compared in terms of trends in the number of approval, special expedited development and review pathways as determined by the FDA, cancer types, line of treatment, trial design features.

Results: We identified 62 SMKI cancer drugs with 150 indications approved by the FDA between 2001 and 2021. Of these, 55 indications (36.7%) were CDG biomarker-directed. There was a significant increase of 20.5% per year in the number of approved CDG biomarker-directed indications. CDG biomarker-directed indications were associated with significantly higher odds in receiving accelerated approval (odds ratio [OR] = 2.728; 95% CI, 1.246 to 5.973; $P = .012$), designating orphan drug (OR = 3.952; 95% CI, 1.758 to 8.883; $P < .001$) and in solid cancer (OR = 7.613; 95% CI, 2.958 to 19.590; $P < .001$), and were associated with significantly lower odds in using randomized controlled trials (RCTs) (OR = 0.103; 95% CI, 0.032 to 0.338; $P < .001$) with less number of entered patients. In solid cancer, CDG biomarker-directed indications were associated with significantly higher overall response rates (ORRs).

Conclusion: The number of CDG biomarker-directed indications in approved SMKIs increased significantly in past two decades, with higher proportion of approvals using special expedited development and approval pathways at the FDA, less proportion of trials with RCT, less number of entered patients but better ORRs.

Background

Cancer is a disease of the genome [1]. Cancer driver gene (CDG) is identified as a kind of oncogenic kinase gene that determines cancer initiation, development, progression and maintenance [1–5]. In 2015, the US Precision Medicine Initiative (PMI) was launched to accelerate progress toward a new era of precision medicine [6–9]. Targeting on cancer driver gene is now leading to a revolutionary breakthrough development not only in precision medicine for patients with malignancies, but also in the strategy to develop small molecular kinase inhibitors (SMKIs) for cancer therapy [2, 4, 10]. By the end of 2021, there are more than 60 chemically synthesized SMKIs approved by the US Food and Drug Administration (FDA) for cancer therapy, leading to significant clinical improvements in treatment of the serious and life-threatening diseases and giving a hope to prolong life for the patients [10–12].

Pivotal trial that demonstrates efficacy and safety has been considered by the FDA as the critical evidence for approval of the indication [13, 14]. In cancer therapy, an indication can be precisely defined by a certain mutated gene, which is screened as a biomarker [1, 2, 8]. In SMKI development, a CDG is serving as the best functional target in pharmaceutical strategy and usually considered as the optimal

genotype-directed biomarker for screening the matched subjects in clinical trials [1, 2]. For example, RET is a cancer driver gene of tyrosine kinase and is a gene-based screening biomarker for RET-positive patients with non-small cell lung cancer (NSCLC) [15, 16]. RET inhibitors such as selpercatinib and pralsetinib got FDA accelerated approvals respectively in indications for patients harboring RET alternation [15, 17, 18]. Pivotal trial evidences for selpercatinib and pralsetinib were both supported by dose-expansion single-arm trials (SATs) [17, 18]. RET gene biomarker was required to pre-screen the patients to fulfill the inclusion criteria of the trials [17, 18]. Nevertheless, the remaining SMKIs do not have CDG biomarkers during their development [2, 12, 19]. The CDG biomarker screening is not required in pivotal trials and approved indications in the drug label. For example, the indications of sorafenib were approved in treating patients without requirement of CDG biomarker detection [20, 21]. Randomized controlled trials (RCTs) are usually used to support the FDA approvals of these indications [20, 21].

Advances in next-generation sequencing (NGS) technology have led to the identification of more than five hundred candidates of CDGs [1, 2, 22, 23]. Patients with the same cancer type are actually be heterogeneous and harbor different CDGs [8, 23]. Treatments for these patients are usually different due to the CDG. For example, according to the Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NSCLC in 2022, seven CDGs have been identified in NSCLC [24]. NSCLC patients may harbor one of CDGs such as EGFR, ALK or ROS1 individually and would be respectively recommended to receive osimertinib for EGFR, lorlatinib for ALK, or entrectinib for ROS1 treatment after CDG screening [25–27]. To date, amount of resources was consumed by CDG-directed SMKI research to develop precision medicine in cancer therapy. However, there are still many new SMKIs developed without CDG biomarker [12, 28, 29]. In this study, we collected the FDA data between 2001 and 2021 to determine whether the characteristics of the indication and pivotal trial of the FDA approved SMKIs with CDG biomarker differ from those without CDG biomarker. We investigated the trend in the number of approvals, expedited development and review programs, quality of pivotal trial evidence, trial design features and trial outcomes. We then compared these characteristics between indications with and without CDG biomarker.

Methods

Sample Identification

All original and supplemental novel drug applications were listed by the FDA on its publicly available FDA's Drugs@FDA database [11]. Our sample included all SMKI cancer drugs, excluding nontherapeutic agents such as diagnostic and contrast agents. One investigator (Y.H.) manually extracted all application approvals of SMKI cancer drugs that occurred between 2001 and 2021 from the database. Initially, application approvals were identified by excluding the approvals that categorized by the FDA as "labeling revisions" or "manufacturing change or addition". Then FDA's letters accompanying the application approvals were examined to identify whether the approvals include a new indication. If one indication was related to two or more updated application approvals, such as "accelerated approval", "new patient population" or "labeling change with clinical data", we counted it as one indication.

Pivotal trials are the clinical trials that serve as the basis of the FDA approval. All pivotal trials that support both the original and supplemental applications were identified. A trial was considered to be pivotal if defined as such in the FDA medical review. If not specify, all efficacy trials that were described as essential to the application approvals were considered to be pivotal.

Data Extraction

Data were extracted by two investigators (Y.H. and L.M.). The following characteristics were collected for each application approvals: year of approval, the FDA's expedited development and review programs or designations (approval pathway [accelerated, not accelerated], breakthrough therapy, fast-track, orphan drug, review type [priority, standard]), type of submission (original, supplemental).

For each application approvals, detailed information on indications was collected: cancer type (solid cancer, hematological malignancies), line of treatment (first, sequential), adjuvant treatment (yes, no), maintenance treatment (yes, no), type of administration (monotherapy, combination) and whether the indication was CDG biomarker-directed. An indication was considered to be directed by CDG biomarker if defined as such in the drug label, that is, the indication focused only on patients with the presence of a specific CDG biomarker as stated in the drug label.

Pivotal trials were identified from the FDA's drug review dossiers and labeling. When more than one pivotal trial supported a single application approval, each trial was considered separately. That is, each approved indication could include one or more pivotal trials to support the application. For each indication, we then selected only one pivotal trial to collect the basic information of the trial and to compare between indications with and without CDG biomarker. The following steps were used to select the pivotal trials. First, we selected the trials that supported the initial application approvals of the indications, that is, trials that supported the postmarketing modifications of the indications were excluded. Second, the trial at the most advanced phase was selected. The collected basic information included: sample size, study design (RCT, non-RCT [SAT]), trial phase (phase I/II, III), type of blinding (double blind, open label), comparator(s) and primary efficacy endpoints. For trials with co-primary endpoints, the most definitive primary endpoint was identified, for example, overall survival (OS) prioritized over progression-free survival (PFS) and PFS over disease response rate.

Efficacy outcomes (including OS, PFS and disease response rate) were collected for all the pivotal trials that support the application approvals. When more than one pivotal trial supported a single application approval, each trial was considered separately and all the trials were selected to collect the efficacy data. If more than one efficacy data was reported for the same outcome in the same trial, most updated result was extracted. For trials assessing OS or PFS, we evaluated whether the efficacy data was clinically meaningful [30]. For all caner types, we considered OS gains of 2.5 months or more and PFS gains of 3 months or more to be clinically meaningful [31].

Statistical Analysis

We used descriptive statistics to characterize the indications and their supporting pivotal trials. To evaluate the number of approved indications over time, we estimated Poisson models with the number of indications as the dependent variable and a linear term for year of approval. The trends were estimated as incidence rate ratios (IRRs) with 95% confidence intervals (CIs). We also analyzed the difference in trends in the mean number of approved indications associated with CDG biomarker versus non-CDG biomarker directed therapeutics.

Indication and pivotal trial characteristics with and without CDG biomarker were compared by using nonparametric Mann-Whitney tests for continuous measures and using the Chi-Square tests for categorical variables. Associations between indication and trial characteristics and CDG biomarker were estimated as odds ratios (ORs) with 95% CIs using logistic regression with univariate model and multivariate models respectively. In the multivariate model 1, we adjusted for cancer type (solid cancer, hematological malignancies). To control potential confounding from type of approval, we additionally adjusted for approval pathway (accelerated, not accelerated) in the multivariate model 2.

Sensitivity analyses were performed to examine the robustness of the associations. First, we repeated our analysis excluding the indications in adjuvant or maintenance setting. Second, we repeated our analysis excluding the indications approved under combination therapy. A p-value less than 0.05 was considered significant. All the analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Trends in the Number of Approved Indications

Between 2001 and 2021, a total of 62 SMKI cancer drugs were approved by the FDA, with 150 indications (Supplementary Table 1). Supplementary Fig. 1 shows the number of approved indications per year with and without CDG biomarker. Fifty-five indications (36.7%) were CDG biomarker-directed (Fig. 1). We observed a significant increase of 20.5% per year (IRR 1.205, 95% CI 1.135 to 1.280, P < 0.001) and 10.3% per year (IRR 1.103, 95% 1.063 to 1.144, P < 0.001), respectively, in the number of approved indications with and without CDG biomarker (P = 0.013 for interaction). The results were consistent in sensitivity analyses (Table 1).

Table 1
Trends in the Number of Approved Indications With and Without CDG Biomarker Between 2001 and 2021

Characteristic	Main analysis		Sensitivity analysis 1		Sensitivity analysis 2	
	Incidence rate ratio (95% CI)	**Interaction**	**Incidence rate ratio (95% CI)**	**Interaction**	**Incidence rate ratio (95% CI)**	**Interaction**
With CDG biomarker	1.205 (1.135 to 1.280)	0.013	1.201 (1.128 to 1.279)	0.012	1.208 (1.127 to 1.296)	0.003
Without CDG biomarker	1.103 (1.063 to 1.144)		1.094 (1.054 to 1.135)		1.070 (1.027 to 1.114)	

Abbreviations:

CDG, caner driver gene; CI, confidence interval; SMKI, small-molecular kinase inhibitor.

Comparison of Indications and Pivotal Trials With and Without CDG Biomarker

In univariate model, indications with CDG biomarker were more frequent among solid cancers compared with hematological malignancies (OR = 5.914; 95% CI, 2.430 to 14.395; *P* < .001) (Table 2 and Table 3). Multivariate model 1 and 2 showed similar results (Table 3). In multivariate model 2, CDG biomarker-directed indications were associated with significantly higher odds in receiving accelerated approval (OR = 2.728; 95% CI, 1.246 to 5.973; *P* = .012), designating orphan drug (OR = 3.952; 95% CI, 1.758 to 8.883; *P* < .001) and initial submission of the application (OR = 2.246; 95% CI, 1.063 to 4.746; *P* = .034). CDG biomarker-directed indications were associated with significantly lower odds in supporting with RCTs (OR = 0.103; 95% CI, 0.032 to 0.338; *P* < .001), phase III (OR = 0.157; 95% CI, 0.053 to 0.464; *P* < .001) and double-blind trials (OR = 0.183; 95% CI, 0.072 to 0.463; *P* < .001), respectively, compared with indications without CDG biomarker. CDG biomarker-directed pivotal trials were associated with significantly higher odds in using disease response rate as primary outcome (OR = 5.568; 95% CI, 1.892 to 16.392; *P* = .002) and lower odds in using PFS as primary outcome (OR = 0.274; 95% CI, 0.114 to 0.658; *P* = .004). The results were consistent in sensitivity analyses (Supplementary Table 2)

Table 2
Characteristics of Indication and Pivotal Trial With and Without CDG Biomarker

Characteristic	With CDG biomarker	Without CDG biomarker	P value
Approval pathway, No. (%)			0.089
Accelerated	25 (45.5)	30 (31.6)	
Not accelerated	30 (54.5)	65 (68.4)	
Breakthrough therapy designation, No. (%)			0.011
Yes	27 (49.1)	27 (28.4)	
No	28 (50.9)	68 (71.6)	
Fast track designation, No. (%)			0.678
Yes	15 (27.3)	23 (24.2)	
No	40 (72.7)	72 (75.8)	
Orphan drug designation, No. (%)			< 0.001
Yes	29 (52.7)	23 (24.2)	
No	26 (47.3)	72 (76.6)	
Review type, No. (%)			0.227
Priority	44 (80.0)	83 (87.4)	
Standard	11 (20.0)	12 (12.6)	
Type of submission, No. (%)			0.003
Initial	36 (65.5)	38 (40.0)	
Supplemental	19 (34.5)	57 (60.0)	
Cancer type, No. (%)			< 0.001
Solid cancer	48 (87.3)	51 (53.7)	
Hematological malignancies	7 (12.7)	44 (46.3)	
First line, No. (%)			0.850
Yes	12 (21.8)	22 (23.2)	
No	43 (78.2)	73 (76.8)	

Abbreviations: CDG, caner driver gene; EFS, event-free survival; DFS, disease-free survival; IQR, interquartile range; PFS, progression-free survival; OS, overall survival; RCT, randomized controlled trial; SAT, single-arm trial.

Characteristic	With CDG biomarker	Without CDG biomarker	P value
Administration			0.979
Monotherapy	41 (74.5)	71 (74.7)	
Combination	14 (25.5)	24 (25.3)	
Adjuvant or maintenance treatment			0.250
Yes	4 (7.3)	2 (2.1)	
No	51 (92.7)	93 (97.9)	
No. of entered patients, Median (IQR)	171 (69 to 399)	312 (111 to 602)	0.025
Type of trial			0.008
non-RCT(SAT)	32 (58.2)	34 (35.8)	
RCT	23 (41.8)	61 (64.2)	
Supported by phase III trials			0.016
Yes	23 (41.8)	59 (62.1)	
No	32 (58.2)	36 (37.9)	
Supported by double blind trials			0.023
Yes	10 (18.2)	34 (35.8)	
No	45 (81.8)	61 (64.2)	
No. of trials supporting approval			0.300
One trial	46 (83.6)	85 (89.5)	
More than one trial	9 (16.4)	10 (10.5)	
Comparator			0.022
Active	13 (23.6)	24 (25.3)	
Add-on	6 (10.9)	15 (15.8)	
Placebo	4 (7.3)	22 (23.2)	
None	32 (58.2)	34 (35.8)	
Use OS as primary outcome			0.634

Abbreviations: CDG, caner driver gene; EFS, event-free survival; DFS, disease-free survival; IQR, interquartile range; PFS, progression-free survival; OS, overall survival; RCT, randomized controlled trial; SAT, single-arm trial.

Characteristic	With CDG biomarker	Without CDG biomarker	P value
Yes	5 (9.1)	11 (11.6)	
No	50 (90.9)	84 (88.4)	
Use PFS/DFS/EFS as primary outcome			0.023
Yes	13 (23.6)	40 (42.1)	
No	42 (76.4)	55 (57.9)	
Use disease response as primary outcome			0.053
Yes	31 (56.4)	38 (40.0)	
No	24 (43.6)	57 (60.0)	

Abbreviations: CDG, caner driver gene; EFS, event-free survival; DFS, disease-free survival; IQR, interquartile range; PFS, progression-free survival; OS, overall survival; RCT, randomized controlled trial; SAT, single-arm trial.

Table 3
Association Between CDG Biomarker and Characteristics of Indication and Pivotal Trial of SMKIs Approved by the FDA between 2001 and 2021

	Univariable analysis		Multivariable analysis (model 1)		Multivariable analysis (model 2)	
Characteristic	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**	**P-value**
Approval pathway						
Not accelerated	0 (Reference)		0 (Reference)		0 (Reference)	
Accelerated	1.806 (0.910 to 3.581)	0.091	2.728 (1.246 to 5.973)	0.012	2.728 (1.246 to 5.973)	0.012
Breakthrough therapy designation						
No	0 (Reference)		0 (Reference)		0 (Reference)	
Yes	2.428 (1.216 to 4.849)	0.012	2.313 (1.108 to 4.827)	0.026	2.039 (0.955 to 4.353)	0.066
Fast track designation						
No	0 (Reference)		0 (Reference)		0 (Reference)	
Yes	1.174 (0.551 to 2.502)	0.678	1.283 (0.569 to 2.891)	0.548	1.436 (0.629 to 3.281)	0.391
Orphan drug designation						
No	0 (Reference)		0 (Reference)		0 (Reference)	
Yes	3.492 (1.721 to 7.084)	< 0.001	4.440 (2.005 to 9.836)	< 0.001	3.952 (1.758 to 8.883)	< 0.001
Review type						
Standard	0 (Reference)		0 (Reference)		0 (Reference)	

Abbreviations: CDG, caner driver gene; CI, confidence interval; FDA, US Food and Drug Administration; IQR, interquartile range; PFS, progression-free survival; OS, overall survival; RCT, randomized controlled trial; SAT, single-arm trial; SMKIs, small-molecular kinase inhibitors.

	Univariable analysis		Multivariable analysis (model 1)		Multivariable analysis (model 2)	
Priority	0.578 (0.236 to 1.417)	0.231	0.689 (0.267 to 1.776)	0.441	0.520 (0.198 to 1.368)	0.186
Type of submission						
Supplemental	0 (Reference)		0 (Reference)		0 (Reference)	
Initial	2.842 (1.424 to 5.672)	0.003	2.572 (1.241 to 5.333)	0.011	2.246 (1.063 to 4.746)	0.034
Cancer type						
Hematological malignancies	0 (Reference)		0 (Reference)		0 (Reference)	
Solid cancer	5.914 (2.430 to 14.395)	< 0.001	5.914 (2.430 to 14.395)	< 0.001	7.613 (2.958 to 19.590)	< 0.001
First line						
No	0 (Reference)		0 (Reference)		0 (Reference)	
Yes	0.926 (0.417 to 2.057)	0.85	0.885 (0.380 to 2.062)	0.777	0.915 (0.386 to 2.166)	0.840
Administration						
Combination	0 (Reference)		0 (Reference)		0 (Reference)	
Monotherapy	0.990 (0.462 to 2.123)	0.979	1.483 (0.658 to 3.345)	0.342	1.214 (0.518 to 2.846)	0.656
Type of trial						
non-RCT (SAT)	0 (Reference)		0 (Reference)		0 (Reference)	
RCT	0.401 (0.203 to 0.791)	0.008	0.110 (0.041 to 0.297)	< .0001	0.103 (0.032 to 0.338)	< 0.001
Supported by phase III trials						

Abbreviations: CDG, caner driver gene; CI, confidence interval; FDA, US Food and Drug Administration; IQR, interquartile range; PFS, progression-free survival; OS, overall survival; RCT, randomized controlled trial; SAT, single-arm trial; SMKIs, small-molecular kinase inhibitors.

	Univariable analysis		Multivariable analysis (model 1)		Multivariable analysis (model 2)	
No	0 (Reference)		0 (Reference)		0 (Reference)	
Yes	0.439 (0.223 to 0.864)	0.017	0.151 (0.061 to 0.376)	< 0.001	0.157 (0.053 to 0.464)	< 0.001
Supported by double to blind trials						
No	0 (Reference)		0 (Reference)		0 (Reference)	
Yes	0.399 (0.179 to 0.890)	0.025	0.155 (0.063 to 0.378)	< 0.001	0.183 (0.072 to 0.463)	< 0.001
No. of trials supporting approval						
One trial	0 (Reference)		0 (Reference)		0 (Reference)	
More than one trial	1.663 (0.631 to 4.384)	0.304	2.165 (0.738 to 6.352)	0.160	1.788 (0.588 to 5.437)	0.306
Comparator						
Active	0.916 (0.422 to 1.988)	0.824	0.928 (0.407 to 2.118)	0.860	1.169 (0.501 to 2.729)	0.719
Add-on	0.653 (0.238 to 1.796)	0.409	0.437 (0.153 to 1.251)	0.123	0.513 (0.174 to 1.512)	0.226
Placebo	0.260 (0.085 to 0.801)	0.019	0.120 (0.037 to 0.384)	< 0.001	0.145 (0.044 to 0.475)	0.001
Use OS as primary outcome						
No	0 (Reference)		0 (Reference)		0 (Reference)	
Yes	0.764 (0.251 to 2.325)	0.635	0.513 (0.162 to 1.624)	0.257	0.671 (0.205 to 2.201)	0.511

Abbreviations: CDG, caner driver gene; CI, confidence interval; FDA, US Food and Drug Administration; IQR, interquartile range; PFS, progression-free survival; OS, overall survival; RCT, randomized controlled trial; SAT, single-arm trial; SMKIs, small-molecular kinase inhibitors.

	Univariable analysis		Multivariable analysis (model 1)		Multivariable analysis (model 2)	
Use PFS as primary outcome						
No	0 (Reference)		0 (Reference)		0 (Reference)	
Yes	0.426 (0.202 to 0.895)	0.024	0.224 (0.098 to 0.513)	< 0.001	0.274 (0.114 to 0.658)	0.004
Use disease response as primary outcome						
No	0 (Reference)		0 (Reference)		0 (Reference)	
Yes	1.937 (0.989 to 3.796)	0.054	6.019 (2.415 to 15.002)	< 0.001	5.568 (1.892 to 16.392)	0.002

Abbreviations: CDG, caner driver gene; CI, confidence interval; FDA, US Food and Drug Administration; IQR, interquartile range; PFS, progression-free survival; OS, overall survival; RCT, randomized controlled trial; SAT, single-arm trial; SMKIs, small-molecular kinase inhibitors.

Comparison of Trial Efficacy Results With and Without CDG Biomarkers

In solid cancer, overall response rates (ORRs) were significantly higher for therapies with CDG biomarker when compared with those without (Median 57.4% [IQR, 40.6–67.4%] *versus* Median 30.0% [IQR, 9.3%-46.9%]; $P < .001$), whereas efficacy results from hematological malignancies did not show the difference (Median 50.0% [IQR, 38.7%-67.6%] *versus* Median 56.0% [IQR, 43.0%-77.5%]; $P = .931$). In solid cancer, there was no statistically significant difference in median PFS gains or in clinically meaningful PFS improvement, respectively, between the therapies with and without CDG biomarker. The median OS gains were longer among therapies with CDG biomarker (21.8 months [IQR, 14.2–32.3 months]) when compared with those without (17.4 months [IQR, 10.8–26.3 months]), despite the results were not statistically significant ($P = .262$) (Table 4). The results were consistent in sensitivity analyses (Supplementary Table 3).

Table 4
Comparison of Pivotal Trial Efficacy Results With and Without CDG Biomarkers

Characteristic	With CDG biomarker	Without CDG biomarker	P-value
Disease response rate, Median (IQR)			
All	57.2 (39.9 to 67.5)	44.1 (26.7 to 59.8)	0.002
Solid cancer[a]	57.4 (40.6 to 67.4)	30.0 (9.3 to 46.9)	< 0.001
Hematological malignancies	50 (38.7 to 67.6)	56 (43.0 to 77.5)	0.931
PFS, Median (IQR)			
All	10.7 (7.3 to 16.5)	9.4 (5.5 to 16.4)	0.565
Solid cancer	10.9 (7.3 to 16.6)	8.6 (5.5 to 16.4)	0.277
Hematological malignancies	5.5 (2.8 to 8.2)	16.4 (14.1 to 19.4)	NE
Clinically meaningful improvement of PFS, No. (%)			
All	21 (77.8)	38 (77.6)	0.982
Solid cancer	20 (80.0)	35 (76.1)	0.706
Hematological malignancies	1 (50.0)	3 (100.0)	NE
OS, Median (IQR)			
All	21.8 (14.2 to 32.3)	17.4 (10.8 to 26.3)	0.262
Solid cancer	21.8 (14.7 to 31.4)	16.9 (10.7 to 25.5)	0.118
Hematological malignancies	42.0 (9.3 to 74.7)	37.3 (33.9 to 40.6)	NE
Clinically meaningful improvement of OS, No. (%)			
All	11 (73.3)	12 (48.0)	0.117
Solid cancer	9 (69.2)	11 (45.8)	0.173
Hematological malignancies	2 (100.0)	1 (100.0)	NE

Abbreviations: CDG, caner driver gene; IQR, interquartile range; NE, not estimable; PFS, progression-free survival; OS, overall survival.

[a] Overall response rates were compared.

Discussion

In this study, we provided a profile of 150 indications of 62 SMKIs approved by the FDA between 2001 and 2021. Our characterization of the indications and pivotal trials between cancer therapies with and without CDG biomarker demonstrated that there was wide variation, respectively, in the numbers of approvals per year, the FDA's expedited development and approval programs, submission type, cancer type, number of entered patients, choice of randomization, double-blinding, comparators and end points. Moreover, we found the ORR was statistically significant higher among therapies with CDG biomarker when compared with those without CDG biomarker.

There are several important findings. First, the number of the FDA approved indications for SMKIs has grown significantly in the past two decades, ranged from one approved indication in the first year to a peak of twenty approved new indications in 2020. The total number was 55 and 95, respectively, for approved indications with and without CDG biomarker. We observed a significantly higher increased trend in the number of CDG biomarker-directed indications between 2011 and 2021. Accumulated evidences showed that the progression of cancer could be significantly inhibited or even partly reversed after blocking the CDG function, for example, osimertinib treatment for NSCLC with EGFR T790M [2, 32, 33]. Additionally, SMKIs show their pharmacological advantages in penetrating the cancer cell membrane with lower research and development cost when compared with antibodies, leading to the boom in CDG therapeutic strategy [34]. CDG directed SMKI development had made great progressions in past decades. Among the 24 approved NSCLC indications, 21 (87.5%) of them were CDG biomarker-directed. With the development of precise treatment and individualized therapy, more CDG biomarkers may be discovered in the future, not only in NSCLC, but also in other cancer types such as liver or kidney carcinoma [6, 8]. According to the findings in this study, BRAF, EGFR, RET and ALK were the most commonly used CDG biomarkers. To date, CDG directed SMKI therapeutics in cancer has become the fastest growing field, suggesting its important role in leading the precise and individual therapy for cancer patients.

Second, we characterized the indications and pivotal trials with and without CDG biomarker. 58.2% (32/55) of CDG biomarker-directed indications were supported with SATs while only 35.8%(34/95) of non-CDG biomarker-directed indications were supported with SATs. In general, SATs would have smaller sample size, and thus spend less time and resources when compared with that of RCTs [35]. This study found that the median number of entered patients was 171 in CDG biomarker-directed trials while the median number was 312 in trials without directed CDG biomarker. In addition, only 7.3%(4/55) of CDG biomarker-directed indications were supported by trials with placebo controls. CDG biomarker-directed indications were significantly more frequent among the FDA's expedited development and approval programs including accelerated approval, breakthrough therapy designation, orphan drug designation and initial submission of the application. By precisely defining entered patients using the CDG biomarker, sample size could be smaller with shorter conducting period facilitating the candidate SMKI development [7, 8]. Anticancer drug trials are increasingly competing in the limited clinical resources [6–9]. Our study illustrated that CDG biomarker-directed SMKI in precision cancer medicine development had advantages in FDA review pathways and spent less clinical resources, suggesting saving time and cost.

Third, results in this study showed that the efficacy outcomes in pivotal trials with CDG biomarker were significantly better when compared with those without CDG biomarker. In solid cancer, CDG biomarker-directed trials had statistically significantly higher ORRs (median 57.4%) when compared with those of non-CDG biomarker-directed trials (median 30%). Possibly due to small sample size, we did not identify significant difference on disease response rate between CDG biomarker-directed trials and non-CDG biomarker-directed trials in hematological malignancies. CDG biomarker-directed trials seem to have better outcome in clinically meaningful improvement for both OS and PFS when compared with those non-CDG biomarker-directed trials. The median OS was 21.8 month *versus* 16.9 month for solid cancer and was 42.0 month *versus* 37.3 month for hematological malignancies, respectively, for trials with and without CDG biomarker. With more number of CDG biomarker-directed trials conducted in the future, we believe that the statistical power will be large enough to detect significantly clinically meaningful improvements.

In conclusion, this study fills a crucial knowledge gap regarding the characteristics of the approved indication of SMKIs and supporting pivotal trials with and without CDG biomarker. The findings in this study would provide significant evidences for precision medicine development of cancer therapy in the future. Tumor is a genetic disease. It is the result of genetic mutation [1, 2]. CDG is both a biomarker and a functional drug target [1, 2, 5]. With the advances of NGS technology, we believe that more number of CDG will be identified to contribute to precision medicine in the future [23]. Since the cancer classification are increasingly subdivided due to different CDGs [3, 8, 23], the number of patients tailored based on the CDGs will become small in each treatment group [8]. Therefore, the CDG biomarker-directed indications are usually eligible for the application of orphan drugs [35]. We believe that more and more number of SMKI agents will be developed based on evidences from phase I/II (dose escalation and dose expansion) SATs in the future [14]. There will be more frequent using of special expedited development and approval programs at the FDA for CDG biomarker-directed pharmaceutical agents. The present study has already identified this trend. Precision medicine is now changing the research and development (R&D) for new pharmaceutical agent. With shorter time to approval and higher clinical benefits [34, 36], the pace for R&D in CDG biomarker-directed agent is continuously speeding up, allowing the optimal subgroup of patients to receive the optimal therapy in the shortest time. This study has provided useful historical references to authority regulators, R&D scientists and other decision makers.

Limitations

Three limitations should be noted. First, some characteristics such like trial duration and safety event were not consistently reported in the FDA publicly available documents and trial reports. Second, the comparisons between indications with and without CDG biomarker are underpowered to detect statistically significant differences on effect sizes of median OS and PFS. Third, the resources were limited to those materials presented by the FDA and did not include information from other agency such as European Medicines Agency (EMA).

Conclusions

Among approved indications of SMKI cancer drugs, indications with CDG biomarkers outweigh those without CDG biomarkers in increasing trend in the number of approvals per year and using special expedited development and approval pathways at the FDA, with lower frequent of using RCTs, less number of entered patients and better efficacy in disease response rates.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

This study was based on publicly available information and involved no patient records. All data generated or analyzed during this study are included in this manuscript and supplementary online content.

Competing interests

The authors declare that they have no competing interests in this section.

Funding

This work was supported by The National Natural Science Foundation of China (Grant No. 82104133).

Authors' contributions

Conceptualization and Funding acquisition: YH. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: YH. Critical revision of the manuscript for important intellectual content: YH, WX. Statistical analysis: YH. Administrative, technical, or material support: YH, WX. Supervision: YH, LM, HW.

Acknowledgements

We thank Jiaying Yan, Beijing University of Chinese Medicine, for assisting in data extraction of the manuscript.

References

1. Martínez-Jiménez F, Muiños F, Sentís I, Deu-Pons J, Reyes-Salazar I, Arnedo-Pac C, Mularoni L, Pich O, Bonet J, Kranas H *et al*. A compendium of mutational cancer driver genes. Nat Rev Cancer. 2020;20(10):555–572. https://doi.org/10.1038/s41568-020-0290-x.
2. Hyman DM, Taylor BS, Baselga J. Implementing genome-driven oncology. Cell. 2017;168(4):584–599. https://doi.org/10.1016/j.cell.2016.12.015.
3. Mateo J, Chakravarty D, Dienstmann R, Jezdic S, Gonzalez-Perez A, Lopez-Bigas N, Ng CKY, Bedard PL, Tortora G, Douillard JY *et al*. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Ann Oncol. 2018;29(9):1895–1902. https://doi.org/10.1093/annonc/mdy263.
4. Zehir A, Benayed R, Shah RH, Syed A, Middha S, Kim HR, Srinivasan P, Gao J, Chakravarty D, Devlin SM *et al*. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med. 2017;23(6):703–713. https://doi.org/10.1038/nm.4333.
5. Tokheim CJ, Papadopoulos N, Kinzler KW, Vogelstein B, Karchin R. Evaluating the evaluation of cancer driver genes. Proc Natl Acad Sci U S A. 2016;113(50):14330–14335. https://doi.org/10.1073/pnas.1616440113.
6. Parikh RB, Schwartz JS, Navathe AS. Beyond genes and molecules - a precision delivery initiative for precision medicine. N Engl J Med. 2017;376(17):1609–1612. https://doi.org/10.1056/NEJMp1613224.
7. Lyman GH, Moses HL. Biomarker tests for molecularly targeted therapies–the key to unlocking precision medicine. N Engl J Med. 2016;375(1):4–6. https://doi.org/10.1056/NEJMp1604033.
8. Jameson JL, Longo DL. Precision medicine–personalized, problematic, and promising. N Engl J Med. 2015;372(23):2229–2234. https://doi.org/10.1056/NEJMsb1503104.
9. Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med. 2015;372(9):793–795. https://doi.org/10.1056/NEJMp1500523.
10. Attwood MM, Fabbro D, Sokolov AV, Knapp S, Schiöth HB. Trends in kinase drug discovery: targets, indications and inhibitor design. Nat Rev Drug Discov. 2021;20(11):839–861. https://doi.org/10.1038/s41573-021-00252-y.
11. US Food and Drug Administration (FDA). Drugs@FDA: FDA approved drug products. Available from: . Accessed February 3, 2022.
12. Bedard PL, Hyman DM, Davids MS, Siu LL. Small molecules, big impact: 20 years of targeted therapy in oncology. Lancet. 2020;395(10229):1078–1088. https://doi.org/10.1016/s0140-6736(20)30164-1.
13. Downing NS, Aminawung JA, Shah ND, Krumholz HM, Ross JS. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005–2012. JAMA Intern Med. 2014;311(4):368–377. https://doi.org/10.1001/jama.2013.282034.
14. Darrow JJ, Avorn J, Kesselheim AS. FDA approval and regulation of pharmaceuticals, 1983–2018. Jama. 2020;323(2):164–176. https://doi.org/10.1001/jama.2019.20288.
15. Wang M, Herbst RS, Boshoff C. Toward personalized treatment approaches for non-small-cell lung cancer. Nat Med. 2021;27(8):1345–1356. https://doi.org/10.1038/s41591-021-01450-2.

16. Drilon A, Hu ZI, Lai GGY, Tan DSW. Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes. Nat Rev Clin Oncol. 2018;15(3):151–167. https://doi.org/10.1038/nrclinonc.2017.175.
17. Drilon A, Oxnard GR, Tan DSW, Loong HHF, Johnson M, Gainor J, McCoach CE, Gautschi O, Besse B, Cho BC *et al*. Efficacy of selpercatinib in RET fusion-positive non-small-cell lung cancer. N Engl J Med. 2020;383(9):813–824. https://doi.org/10.1056/NEJMoa2005653.
18. Gainor JF, Curigliano G, Kim DW, Lee DH, Besse B, Baik CS, Doebele RC, Cassier PA, Lopes G, Tan DSW *et al*. Pralsetinib for RET fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study. Lancet Oncol. 2021;22(7):959–969. https://doi.org/10.1016/s1470-2045(21)00247-3.
19. Hofmann F, Hwang EC, Lam TB, Bex A, Yuan Y, Marconi LS, Ljungberg B. Targeted therapy for metastatic renal cell carcinoma. Cochrane Database Syst Rev. 2020;10(10):CD012796. https://doi.org/10.1002/14651858.CD012796.pub2.
20. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, de la Fouchardiere C, Pacini F, Paschke R, Shong YK *et al*. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet. 2014;384(9940):319–328. https://doi.org/10.1016/s0140-6736(14)60421-9.
21. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A *et al*. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378–390. https://doi.org/10.1056/NEJMoa0708857.
22. Flaherty KT, Gray RJ, Chen AP, Li S, McShane LM, Patton D, Hamilton SR, Williams PM, Iafrate AJ, Sklar J *et al*. Molecular landscape and actionable alterations in a genomically guided cancer clinical trial: National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH). J Clin Oncol. 2020;38(33):3883–3894. https://doi.org/10.1200/jco.19.03010.
23. Ziogas DE, Kyrochristos ID, Roukos DH. Next-generation sequencing: from conventional applications to breakthrough genomic analyses and precision oncology. Expert Rev Med Devices. 2018;15(1):1–3. https://doi.org/10.1080/17434440.2017.1419059.
24. Non-Small Cell Lung Cancer. NCCN Guidelines. January 2022. Available from: . Accessed February 20, 2022.
25. Wu YL, Tsuboi M, He J, John T, Grohe C, Majem M, Goldman JW, Laktionov K, Kim SW, Kato T *et al*. Osimertinib in resected EGFR-mutated non-small-cell lung cancer. N Engl J Med. 2020;383(18):1711–1723. https://doi.org/10.1056/NEJMoa2027071.
26. Shaw AT, Bauer TM, de Marinis F, Felip E, Goto Y, Liu G, Mazieres J, Kim DW, Mok T, Polli A *et al*. First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. N Engl J Med. 2020;383(21):2018–2029. https://doi.org/10.1056/NEJMoa2027187.
27. Drilon A, Siena S, Dziadziuszko R, Barlesi F, Krebs MG, Shaw AT, de Braud F, Rolfo C, Ahn MJ, Wolf J *et al*. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three

phase 1–2 trials. Lancet Oncol. 2020;21(2):261–270. https://doi.org/10.1016/s1470-2045(19)30690-4.

28. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J *et al*. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391(10126):1163–1173. https://doi.org/10.1016/s0140-6736(18)30207-1.
29. Rini BI, Pal SK, Escudier BJ, Atkins MB, Hutson TE, Porta C, Verzoni E, Needle MN, McDermott DF. Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomised, controlled, open-label study. Lancet Oncol. 2020;21(1):95–104. https://doi.org/10.1016/s1470-2045(19)30735-1.
30. Ellis LM, Bernstein DS, Voest EE, Berlin JD, Sargent D, Cortazar P, Garrett-Mayer E, Herbst RS, Lilenbaum RC, Sima C *et al*. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol. 2014;32(12):1277–1280. https://doi.org/10.1200/jco.2013.53.8009.
31. Kumar H, Fojo T, Mailankody S. An appraisal of clinically meaningful outcomes guidelines for oncology clinical trials. JAMA Oncol. 2016;2(9):1238–1240. https://doi.org/10.1001/jamaoncol.2016.0931.
32. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphunkul A, Imamura F, Nogami N, Kurata T *et al*. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med. 2018;378(2):113–125. https://doi.org/10.1056/NEJMoa1713137.
33. Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, Zhou C, Reungwetwattana T, Cheng Y, Chewaskulyong B *et al*. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. N Engl J Med. 2020;382(1):41–50. https://doi.org/10.1056/NEJMoa1913662.
34. Molto C, Hwang TJ, Borrell M, Andres M, Gich I, Barnadas A, Amir E, Kesselheim AS, Tibau A. Clinical benefit and cost of breakthrough cancer drugs approved by the US Food and Drug Administration. Cancer. 2020;126(19):4390–4399. https://doi.org/10.1002/cncr.33095.
35. Kesselheim AS, Myers JA, Avorn J. Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer. JAMA Intern Med. 2011;305(22):2320–2326. https://doi.org/10.1001/jama.2011.769.
36. Hwang TJ, Franklin JM, Chen CT, Lauffenburger JC, Gyawali B, Kesselheim AS, Darrow JJ. Efficacy, safety, and regulatory approval of Food and Drug Administration-designated breakthrough and nonbreakthrough cancer medicines. J Clin Oncol. 2018;36(18):1805–1812. https://doi.org/10.1200/jco.2017.77.1592.

Figures

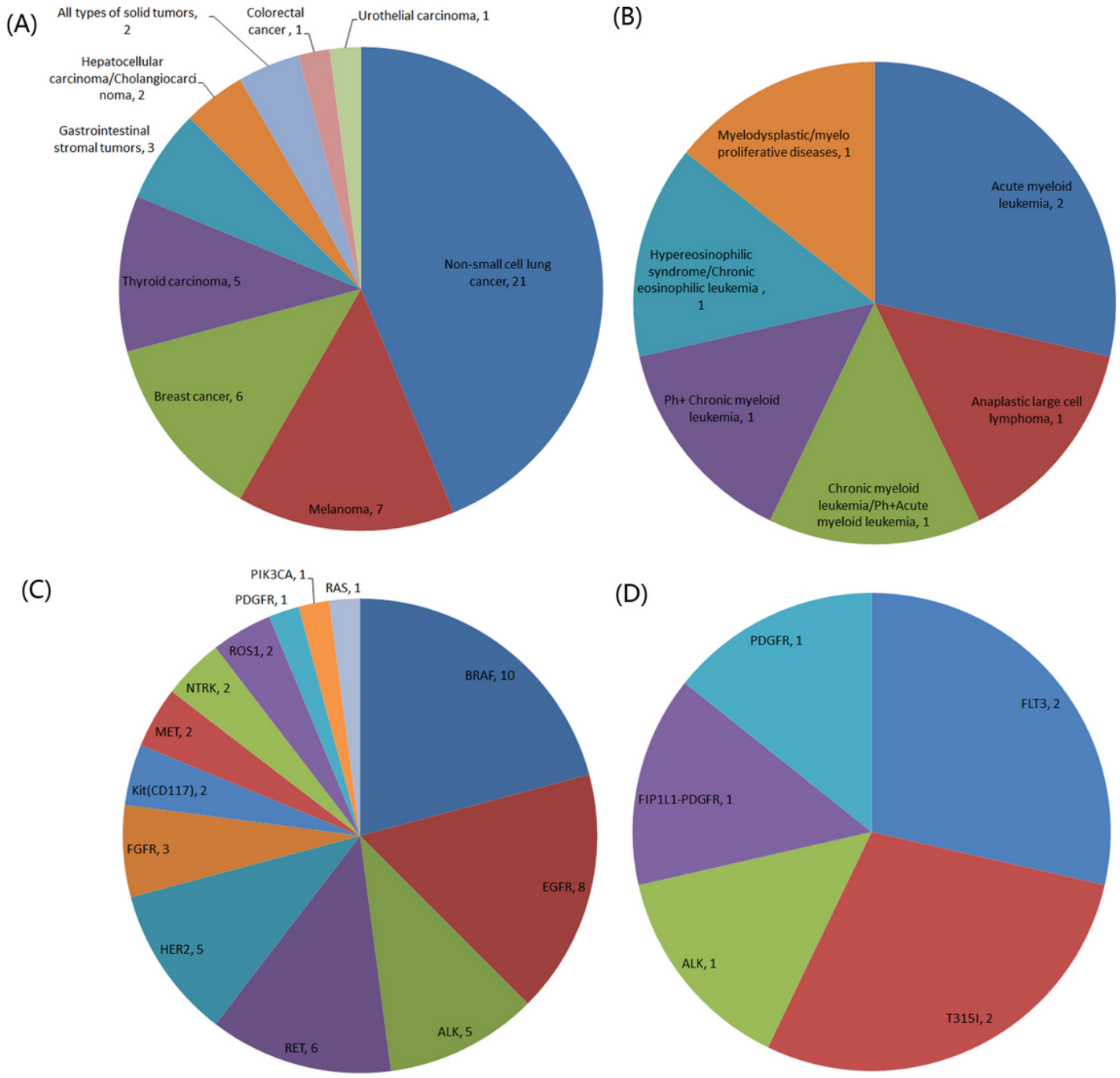

Figure 1

Distribution in the Number of CDG Biomarker-directed Indications (A) By types of solid cancer; (B) By types of hematological malignancies; (C) By types of biomarker in solid cancer; (D) By types of biomarker in hematological malignancies

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Onlineonlymaterial.docx