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Characteristics of trials and regulatory pathways leading to US approval of innovative vs. non-innovative oncology drugs

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ABSTRACT

Background: Successful first-generation drugs can be converted with small alterations to ‘second-generation drugs,ẅhich are cheaper to develop and may pose less financial risk for manufacturers due to already validated action mechanism and a well-defined consumer market.
Methods: We found four classes of cancer drugs for first- and second generation products approved in the US: BCR-ABL tyrosine kinase inhibitors (TKI) for treatment of CML, ALK + TKI for NSCLC, CD20 monoclonal antibodies for CLL, and HER2 monoclonal antibodies for breast cancer. We analyzed the characteristics of the clinical trials and the approval pathways for these 14 drugs.
Results: First-generation and 4 out of 5 s-generation BCR-ABL TKI drugs were granted expedited approval, while all drugs were approved based on single-arm trials. Both ALK + TKI drugs were based on single-arm trials and expedited approval. The first-generation CD20 monoclonal antibody drug was approved based on single-arm trials, and one of the second-generation drugs had pivotal trials that were randomized. All benefited from expedited approval. All HER2 monoclonal antibodies in the sample were based on randomized trials and expedited pathways.
Conclusion: Second-generation TKI and monoclonal antibodies were often approved through expedited regulatory pathways and studied in single-arm trials. This helps to facilitate the approval for earlier use by patients, but is also associated with greater risk of post-approval safety-related labeling changes or unanticipated adverse events.

1. Introduction

Innovative drugs are rightly given special attention by the US Food and Drug Administration (FDA) [1–4]. First-in-class products—particularly those treating serious or life-threatening diseases—are often quite innovative and many qualify for special drug approval pathways that have been designed to speed the development and review of drugs treating serious or life-threatening diseases [5]. These pathways include the priority review program (first created in 1992) that enables FDA review in 6 months (vs. 10 months for standard review), the accelerated review program (1992) that permits approval based on surrogate measures (a biomarker or some other measurement, rather than patient symptoms or health outcomes) only reasonably likely to predict clinical endpoints and the fast-track program (1997) and breakthrough therapy program (2012) that are intend to reduce the duration of pre-approval clinical trials [2,6–10]. In part as a result of these expedited pathways, for example, a transformative, first-in-class drug like imatinib (Gleevec) was approved for use in patients with chronic myelogenous leukemia (CML) just 2.5 years after clinical trials were started, as compared to the average clinical trial period of about 6–7 years [11–13].

After a new drug is launched and is successful, the active ingredient may be updated by the manufacturer, or copied with small alterations by other manufacturers, to create so-called “second-generation” drugs [14]. Second-generation drugs are in the same drug class (and may even be the same active ingredient) and treat the same condition as the original innovator drug, although they may be adjusted in ways that make the drug incrementally more effective or safe, treat versions of the disease resistant to the first-in-class drug, or improve dosing convenience for patients. In

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other cases, second-generation drugs provide no measurable clinical benefits over innovator products. Second-generation products are often much less expensive to develop and carry different financial risk for the manufacturer as compared to the original innovative product, because the mechanism of action has now been validated and a well-defined consumer market already exists. However, in the US, the second generation products are often priced as high as, or higher than, the first generation drugs [15].

Are first- and second-generation drugs handled differently by US regulators? Previous studies showed that first-in-class products are characterized by faster review times than subsequent entrants in the same class [16,17]. We do not know how the clinical trials needed to approve first- and second-generation drugs differ, or to what extent second-generation treatments benefit from FDA's expedited review and development pathways. We investigated these issues within four different classes of cancer drugs.

2. Methods

2.1. Study drugs

We evaluated a list of all cancer drugs approved in the US from 1994 to 2016 to determine examples of secondary innovation among cancer therapeutics. We looked for drugs approved with a novel mechanism of action that were followed by approvals of other drugs with the same mechanism of action for which the critical stages of their development appeared to begin after approval of the first-generation drug and which targeted the same indication. We defined these as second-generation treatments.

2.2. Data extraction

Among all first-generation and second-generation study drugs, we identified medical reviews from Drugs@FDA and noted any special regulatory pathways for which they qualified. We then isolated the FDA-designated pivotal trials that provided the key efficacy data supporting drug approval and extracted the approved disease indication, trial characteristics, and major efficacy outcome measures. With regard to the regulatory approval pathway, we distinguished between standard approval pathway and one of the expedited review pathways, which are intended to encourage the development and speed the evaluation of innovative products to meet serious unmet health needs [2].

We extracted the following trial features: design (randomized vs. single-arm), observed outcomes, and number of patients enrolled. We also considered the major efficacy outcomes evaluated, focusing on whether the outcome was a surrogate measure (for example, progression free survival or cytogenetic response) or overall survival (a clinical outcome).

3. Results

Four classes of oncology products met our inclusion criteria: tyrosine kinase inhibitors for *BCR-ABL* rearrangements in CML, tyrosine kinase inhibitors for *ALK*+ non-small cell lung cancer, monoclonal antibodies against CD20 for treatment of chronic lymphocytic leukemia (CLL), and monoclonal antibodies against *HER2* for treatment of breast cancer. Our sample included four first-generation products and nine second-generation products (Tables 1 and 2).

3.1. BCR-ABL *tyrosine kinase inhibitors for CML*

The FDA approved imatinib in 2001. It benefited from the fast track, accelerated approval, and priority review designations based on the drug's striking results in treating patients with CML in its earliest clinical trials [18–20]. Four products in this category met our criteria for second-generation products, approved from 2006-2016. While dasatinib (Sprycel), nilotinib (Tasigna), and ponatinib (Iclusig) were granted an expedited program by the FDA, bosutinib (Bosulif) was reviewed under the standard drug approval pathway.

Imatinib's approval was based on three pivotal single-arm trials in which in total 1027 patients received imatinib after failure with the standard of care at the time (interferon). It included a single-arm study and demonstrated a clinically relevant improvement in hematologic response.

As shown in Table 1, the four second-generation drugs in this category were also approved based on single-arm studies (four single-arm studies regarding dasatinib, while the approval of nilotinib, bosutinib, and ponatinib was based one single-arm study). The pivotal trial endpoints for the second-generation drugs were major cytogenetic response or major hematologic response.

3.2. ALK+ *tyrosine kinase inhibitors for non-small-cell lung cancer*

Crizotinib (Xalkori) was FDA-approved for *ALK*+ non-small cell lung cancer after progression on first line therapy in 2011 after designation for the fast track, accelerated approval, and priority review. The FDA approved the second-generation drugs ceritinib (Zykadia) in 2014 and alectinib (Alecensa) in 2015. Both drugs also qualified for expedited review pathways: ceritinib received accelerated approval, priority review, and breakthrough therapy while alectinib was granted accelerated approval.

Crizotinib's approval was based on two multi-center, single-arm studies that enrolled 255 patients after undergoing prior systematic therapy. The studies demonstrated a clinically relevant improvement in the objective response rate according to Response Evaluation Criteria in Solid Tumors (RECIST), i.e. the measurement of the tumor size with imaging results.

Ceritinib was approved based on one trial including 163 patients. The key inclusion criteria were progression on or intolerance to crizotinib. The overall response rate according to RECIST served as the efficacy endpoint. Alectinib had the same inclusion criteria for patients resistant or intolerant to treatment with crizotinib and its approval was based on two single-arm studies, including 87 and 138 patients. In both studies, objective response rate was the major efficacy endpoint. Alectinib has also been approved for previously untreated ALK-positive patients with metastatic NSCLC. This approval was based on a randomized study with PFS as major efficacy endpoint.

3.3. CD20 *monoclonal antibodies for CLL*

In 1997, the FDA approved rituximab (Rituxan) for CLL through priority review. Rituximab's approval was based on two single-arm studies including 203 patients with relapsed or refractory B-cell NHL. Clinical improvement was measured with the overall response rate.

There have since been two second-generation drugs in this category, approved in 2009 and 2013. Ofatumumab (Arzerra) was granted accelerated approval and priority review while Obinutuzumab (Gazyva) was approved through priority review and breakthrough therapy. The pivotal trial for ofatumumab was a single-arm multicenter study in which 154 patients were administered ofatumumab with the objective tumor response rate as the major efficacy outcome endpoint.

By contrast, the most recent second-generation drug in this category, obinutuzumab (Gazyva), was approved based on a randomized three-arm study. The study had an open-label design and

Table 1
Characteristics of First- and Second-Generation Tyrosine Kinase Inhibitor Drugs.

Drug name	First-generation		Second-generation					
	Imatinib (Gleevec)	Crizotinib (Xalkori)	Dasatinib (Sprycel)	Nilotinib (Tasigna)	Bosutinib (Bosulif)	Ponatinib (Iclusig)	Ceritinib (Zykadia)	Alecensa (Alectinib Hydrochloride)
Year of approval	2001	2011	2006	2007	2012	2012	2014	2015
Molecular target	BCR-ABL	ALK	BCR-ABL	BCR-ABL	BCR-ABL	BCR-ABL	ALK	ALK
Special regulatory pathways	AA, PR, FT	AA, PR, FT	PR, FT	AA	None	AA, PR, FT	AA, PR, BT	AA
Initial indication	CML	NSCLC	CML	CML	CML	CML	NSCLC	NSCLC
Study design	Three single-arm studies	Two single-arm studies	Four single-arm studies	Single-arm study	Single-arm study	Single-arm study	Single-arm study	Previously treated patients: Two single-arm studies Previously untreated patients: One randomized study.
Patient population	Study 1: chronic phase Study 2: accelerated phase Study 3: myeloid blast crisis	Study 1 and study 2: Patients with prior systemic therapy (with exception of 15 patients)	Patients resistant or intolerant to treatment with imatinib Study 1: chronic phase Study 2: accelerated phase Study 3: myeloid blast phase Study 4: lymphoid blast phase	Patients resistant or intolerant to treatment with imatinib with separate cohorts for chronic and accelerated phase	Patients previously treated with one prior TKI (imatinib) or more than one TKI (imatinib) followed by dasatinib or nilotinib	Patients resistant or intolerant to TKI therapy	Patients resistant or intolerant to treatment with crizotinib	1. Patients resistant or intolerant to treatment with crizotinib. 2. Previously untreated ALK-positive metastatic NSCLC patients; arm 1: Alecensa; arm 2: crizotinib
Number of participants	Study 1: 532 Study 2: 235 Study 3: 260	Study 1: 136 Study 2: 119	Study 1: 186 Study 2:107 Study 3: 74 Study 4: 78	Chronic phase: 280 Accelerated phase: 105	546	444	163	Previously treated patients: Study 1: 87 patients Study 2: 138 patients Previously untreated patients: PFS
Major efficacy endpoint	Hematologic response	Study 1: ORR Study 2: ORR	Cytogenetic response	Chronic phase: cytogenetic response Accelerated phase: hematologic response	Cytogenetic response	Cytogenetic response, hematologic response	ORR	Previously treated patients: Study 1: ORR Study 2: ORR Previously untreated patients: PFS
Outcome	Study 1: 88% Study 2: 63% Study 3: 26%	Study 1: 50% Study 2: 61%	Study 1: 45% Study 2: 31% Study 3: 30% Study 4: 50%	Chronic phase: 40% Accelerated phase: 26%	Between 51.4% and 52.8%	Cytogenetic response: 54% (chronic phase) Hematologic response: between 41% and 52% (accelerated or blast phase)	43.6%	Previously treated patients: Study 1: 38% Study 2: 44% Previously untreated patients: Increase in median PFS of 15.3 months.

AA = accelerated approval; PR = priority review; FT = fast-track; BT = breakthrough therapy; CML = chronic myelogenous leukemia; NSCLC = non-small cell lung cancer; ALL = acute lymphocytic leukemia; ORR = objective response rate.

Table 2
Characteristics of First- and Second-Generation Monoclonal Antibodies.

Drug name	First-generation		Second-generation			
	Rituximab (Rituxan)	Trastuzumab (Herceptin)	Ofatumumab (Arzerra)	Obinutuzumab (Gazyva)	Pertuzumab (Perjeta)	Trastuzumab emtansine (Kadcyla)
Year of approval	1997	1998	2009	2013	2012	2013
Mechanism of action	CD20 mAb	HER2 mAb	CD20 mAb	CD20 mAb	HER2 mAb	HER2 mAb
Special regulatory pathways	PR	PR, FT	AA, PR	PR, BT	PR	PR, FT
Initial indication	CLL	Breast cancer	CLL	CLL	Breast cancer	Breast cancer
Study designs	Two single-arm studies	Study 1: randomized study Study 2: single-arm study	Single-arm study	Randomized, three-arm study	Randomized study	Randomized study
Patient population	Patients with relapsed or refractory CLL	Study 1: patients who had not been previously treated with chemotherapy were randomized to receive either chemotherapy alone or in combination with trastuzumab Study 2: patients were treated with trastuzumab alone	Patients with relapsed CLL or refractory to rituximab, fludarabine and/or alemtuzumab	Patients previously untreated with coexisting medical conditions or reduced renal function - Arm 1: chlorambucil control - Arm 2: obinutuzumab + chlorambucil - Arm 3: rituximab + chlorambucil	Patients randomly allocated to receive placebo plus trastuzumab and docetaxel or pertuzumab plus trastuzumab and docetaxel	Patients with prior taxane or trastuzumab therapy randomly allocated to receive lapatinib plus capecitabine or trastuzumab emtansine
Number of participants	Study 1: 166 Study 2: 37	Study 1: 469 Study 2: 222	154	356	808	991
Major efficacy endpoint	Study 1: ORR Study 2: ORR	Study 1: median time to disease progression Study 2: ORR	ORR	PFS	PFS	PFS
Outcome	Study 1: between 53% and 78% Study 2: 46%	Study 1: 7.2 months for trastuzumab plus chemotherapy and 4.5 months for chemotherapy alone Study 2: between 4% and 17%	42%	Arm 1: 11.1 months Arm 2: 23 months Arm 3: 23 months	Increase in median PFS of 6.1 months	Increase in median PFS of 3.2 months

AA = accelerated approval; PR = priority review; FT = fast-track; BT = breakthrough therapy; CLL = chronic lymphocytic leukemia; ORR = objective response rate; PFS = progression-free survival.

Table 3
Date of Approval in the EU and the US.

	Drug name	Approval Date US (FDA)	Approval Date EU (EMA)	Days between US and EU approval
First-generation TKI	Imatinib (Gleevec)	10 May 2001	7 November 2001	181
	Crizotinib (Xalkori)	26 August 2011	23 October 2012	423
	Dasatinib (Sprycel)	28 June 2006	20 November 2011	1966
Second-generation TKI	Nilotinib (Tasigna)	29 October 2007	19 November 2007	21
	Bosutinib (Bosulif)	4 September 2012	26 March 2013	204
	Ponatinib (Iclusig)	14 December 2012	1 July 2013	199
	Ceritinib (Zykadia)	29 April 2014	6 May 2015	371
	Alectinib Hydrochloride (Alecensa)	11 December 2015	16 February 2017	432
First-generation monoclonal antibodies	Rituximab (Rituxan)	26 November 1997	2 June 1998	191
	Trastuzumab (Herceptin)	25 September 1998	28 August 2000	702
	Ofatumumab (Arzerra)	26 October 2009	19 April 2010	175
Second-generation monoclonal antibodies	Obinutuzumab (Gazyva)	1 November 2013	22 July 2014	263
	Pertuzumab (Perjeta)	8 June 2012	4 March 2013	259
	Trastuzumab emtansinse (Kadcyla)	22 February 2013	15 November 2013	266

EU = European Union; TKI = tyrosine kinase inhibitors; US = United States.

demonstrated a clinically relevant improvement in progression-free survival.

3.4. HER2 *monoclonal antibodies for breast cancer*

The FDA approved trastuzumab (Herceptin) to treat metastatic *HER2* positive breast cancer in 1998. It qualified for fast track and the priority review designations. Approval was based on an open-label study (222 patients) and a randomized trial (469 patients). In latter trial, patients who had not been previously treated with chemotherapy were randomized to receive either standard chemotherapy alone or in combination with trastuzumab. Clinical effectiveness was based on the median time to disease progression. In the open-label study, patients were treated with trastuzumab alone and overall response rate served as the major clinical outcome measure.

There have since been two drugs in this category that met our criteria as being second-generation treatments: pertuzumab (Perjeta) approved for use in combination with trastuzumab (Herceptin) and docetaxel (Taxotere) in 2012, and trastuzumab emtansine (Kadcyla) approved in 2013 [21,22]. The latter benefited from priority review and fast track, while pertuzumab was designated as priority review. The pivotal trials of both drugs were randomized. While pertuzumab's study (808 patients) was based on a randomized, double-blind, placebo-controlled study, trastuzumab emtansine's trial (991 patients) was characterized through a randomized, multicenter study. Both pertuzumab and trastuzumab emtansine demonstrated clinically relevant improvement in progression-free survival.

3.5. *Market access in the US and European Union*

All 14 first- and second-generation cancer drugs in our cohort were approved in both the US and EU. In addition, all were first approved in the US and subsequently in the EU (Table 3). The time between US and EU approval varied between 21 days (nilotinib; Tasigna) and 1966 days (dasatinib; Sprycel). The average duration between US and EU approval was 404 days.

4. Discussion

In our review of four classes of oncology drugs approved in the US from 1994 to 2016, first-generation products benefited from expedited development and regulatory review pathways and were often studied in open-label, single-arm studies. These mechanisms helped facilitate widespread availability of the innovative products to patients. We also observed that second-generation products qualified for expedited development and approval pathways and in some cases were also tested in small, single-arm studies. We therefore found important similarities in the clinical testing and regulatory review characteristics applied to two sets of first- and second-generation cancer drugs.

The FDA's expedited development and approval pathways were created to benefit drugs that treat serious or life-threatening diseases or for treatments that demonstrate improvement over available therapy [23–27]. First-generation drugs like trastuzumab and imatinib addressed unmet medical needs and were transformative products. Their pivotal testing demonstrated that they offered substantial advances in therapy for patients with limited treatment options. It was therefore reasonable to facilitate their regulatory approval using single-arm studies with historical controls that could be completed more efficiently. There is by definition less patient demand for follow-on, second-generation products that target the same disease and use the same mechanism of action [2]. Yet drugs in this category still often received expedited regulatory status. These findings are important because expedited pathways can be associated with greater risks of adverse events and safety-related labeling changes after approval [28]. Indeed, in the case of ponatinib, the FDA had to temporarily suspend its use after safety-related issues arose shortly after the drug's initial approval [29].

Many of the second-generation drugs in our sample were also approved based on surrogate measures. Overall survival is a key endpoint for treatment with an oncology drug [24,30,31,32]. However, all second-generation TKI drugs were approved on the basis of surrogates such as cytogenetic, hematologic, or objective response rates. Surrogate measures of drug efficacy can help expedite development, particularly if they are well-correlated with clinical endpoints, and in this case, the endpoints used for these second-generation drugs also matched the endpoints used in approval of the first-generation products. However, cancer drugs approved based on surrogate measures alone should still be followed up closely to ensure that they translate to the expected level of clinical outcomes [33].

It is interesting to note that despite the expedited pathways applied to most of the second-generation products in our sample, and the fact that second-generation products are less costly to develop [2], second-generation oncology drugs in the US are often priced at levels comparable to the first-generation agents, or higher [34]. This is because the price of a drug in the US is based on what the market will bear, and in the case of oncology drugs, many insurers cannot exclude them from formularies, even if they are not priced at a cost-effective level. For example, Medicare Part D considers cancer drugs to be a protected class and requires insurance plans to cover essentially all FDA-approved drugs in the class. These rules prevent payers from negotiating optimally with the manufacturers

of the product in arriving at prices that better reflect the product's value. As a consequence, drug prices are generally higher in the US than in comparable European countries, such as Germany, Switzerland, or the United Kingdom, where drug pricing is more directly regulated by the governments [35,36]. For example, prices for the first-generation drug trastuzumab are $7688 per gram in the US and $5125 per gram in Germany (ex-factory price), and for the second-generation drug trastuzumab emtansine $29,450 per gram in the US and $18,175 per gram in Germany (ex-factory price). First-generation drug rituximab costs $6597 per gram in the US and $1534 in the United Kingdom, while the price for second-generation drug obinutuzumab is $6096 in the US and $4306 in the United Kingdom (ex-factory price) [37].

Our results are consistent with other studies showing an increasing prevalence in recent years of expedited development and review of cancer drugs in general that cannot be attributed to an increase in the number of innovative new drug classes [2,38,39]. Expansion of expedited designations in the US also includes application of the Orphan Drug Act designation—intended to be reserved for rare diseases—to drugs targeting biomarker-defined subsets of more common diseases, including bosutinib (Bosulif), ponatinib (Iclusig), and ceritinib (Zykadia) [40]. We expect these trends to continue, as the FDA and the European Medicines Agency (EMA) have implemented new expedited approval pathways and mechanisms in the past decade, such as the breakthrough therapy in the US or the Conditional Marketing Approval or priority medicines (PRIME) in the EU [41–43].

The anticancer medicines in our cohort were available in the US before the EU, consistent with other studies [44,48]. One possible cause is that the review time for drugs is, in general, longer in the EU than in the US for both, first- and second-generation drugs [44–48]. For example, review time for the first-generation drug crizotinib was 150 days in the US vs. 356 days in the EU, and 126 days in the US vs. 337 days in the EU for the second-generation drug ceritinib [49,47]. Collaborative activities between the FDA and the EMA could help reduce this gap.

Although they are not as innovative as first-generation products, second-generation drugs can be very helpful in treating patients. For example, in our sample, second-generation tyrosine kinase drugs as well as second-generation monoclonal antibodies were tested on patients who were intolerant or resistant to the first-generation options [50]. While the incidence of patients with drug-resistant cancers is smaller than newly-diagnosed patients, it is still important to ensure that second-generation products can be available for patients and that there is sufficient incentive for private investment in such products [50]. Second-generation products can also sometimes offer improvements in bioavailability or reductions in adverse effects. Prospective randomized trials should be conducted to demonstrate whether second-generation products are more effective or safer than first-generation products as first-line therapy.

Notably, clinical testing of second-generation monoclonal antibodies was more rigorous than that of comparable tyrosine kinase inhibitor drugs. While the first-generation drug rituximab was approved based on two single-arm studies and the first-generation drug trastuzumab based on a single-arm study and a randomized study, all second-generation drugs, with the exception of ofatumumab, contained randomized trials with PFS as a clinical outcome measure. Reasons for differences in the formal evaluation of the drugs in this class and second-generation tyrosine kinase inhibitor drugs could be the basis for further study.

Our review of differences between first- and second-generation drug approvals covered only four different drug categories and therefore may not be generalizable to all cancer drugs. In addition, FDA recommendations for levels of evidence to support approval of an oncology product can change over time [51].

Despite these limitations, we found that second-generation tyrosine kinase drugs and monoclonal antibodies were often approved through expedited approval pathways. While various development shortcuts may be reasonable for important new classes of drugs meeting unmet medical needs, they also involve risks to patients [52]. Further study is needed of their implications when applied to second-generation drugs.

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