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BRIEF REPORT

Clinical development time is shorter for new anticancer drugs approved via accelerated approval in the US or via conditional approval in the EU

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Abstract

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) offer expedited regulatory approval programs for drugs with high potential patient value applicable at different stages leading to marketing authorization: (i) drug development (fast track designation (FTD), breakthrough therapy designation (BTD), regenerative medicine advanced therapy designation in the United States, and priority medicines scheme in the European Union), (ii) review of marketing authorization application (priority review in the United States and accelerated assessment in the European Union), (iii) approval of drug (accelerated approval in the United States and conditional approval in the European Union). Typical clinical development time of 76 new anticancer drugs, for which the EMA gave a positive opinion between January 2010 and December 2019, was 6.7 years: 5.8 years for small molecules and 7.7 years for biotechnology-derived products. Drugs following only BTD (5.6 years) typically had a shorter clinical development time than drugs following only FTD (6.4 years) or both FTD and BTD (6.4 years), compared to drugs not following any expedited regulatory approval program at the drug development stage (7.7 years). Drugs following an expedited regulatory approval program at the stage of drug development and accelerated approval in the United States (FDA1 [4.5 years] and FDA3 [5.6 years]), and drugs following the standard procedure at the stage of drug development and conditional approval in the European Union (EMA5 [5.5 years] and EMA7 [4.5 years]) typically had a reduced clinical development time. These findings provide insight for the industry into combinations of expedited regulatory approval programs correlated with shorter clinical development time of new anticancer drugs.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

There are a limited number of publications about the clinical development time of new drugs in the United States. However, no literature exists about the clinical development time of new anticancer drugs in relation to expedited regulatory

approval programs offered by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

WHAT QUESTION DID THIS STUDY ADDRESS?

The correlation between different expedited regulatory approval programs applicable in the United States and the European Union or type of product and the clinical development time of new anticancer drugs.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

It was shown that drugs following only breakthrough therapy designation (BTD) had a shorter clinical development time than drugs following only fast track designation (FTD) or both FTD and BTD, compared to drugs not following any expedited regulatory approval program at the drug development stage. The regulatory pathways applicable in the United States and the European Union correlated with the shortest clinical development time of new anticancer drugs were identified.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

A field of improvement for the regulatory framework in the United States and European Union to enable earlier drug availability was indicated. Insight into combinations of expedited regulatory approval programs correlated with shorter clinical development time of new anticancer drugs was provided for the industry.

INTRODUCTION

In 2020, the Global Cancer Observatory (GLOBOCAN) estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths.[1] New anticancer drugs have been invented with the goal to treat the increasing number of patients with cancer efficiently and safely, decrease the cost of the drugs for the patients, and decrease the cost of development and chance of failure to obtain marketing authorization for the pharmaceutical industry.[2] The cost of developing a new medicine is estimated to range between US $944 million and US $2826 million (adjusted to 2019 prices), including the discovery and preclinical and clinical developments.[3] The rate of failure to obtain marketing authorization decreases when a candidate drug advances from preclinical development phase into phase I and subsequent phases of clinical development. Anticancer drugs in phase I, phase II, and phase III of clinical development at the drug development stage, and at the stage of review of the marketing authorization application (MAA) have been reported to have a 3.4%, 6.7%, 35.5%, and 81.7% chance of receiving regulatory approval in the United States, respectively.[4]

The regulatory agencies in the United States and the European Union, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), respectively, offer expedited regulatory approval programs for drugs with high potential patient value, which:

(i) support the development of such drugs (i.e., fast track designation [FTD; introduced in 1987],[5] breakthrough therapy designation [BTD; introduced in 2012],[5] and regenerative medicine advanced therapy designation [RMATD; introduced in 2017][6] in the United States, and priority medicines scheme [PRIME; introduced in 2016][7] in the European Union),
(ii) provide shorter review times of MAAs (i.e., priority review designation [introduced in 1992][5] in the United States, and accelerated assessment [introduced in 2005][8] in the European Union), or
(iii) provide preliminary approval (i.e., accelerated approval [introduced in 1992][5] in the United States, and exceptional circumstances [introduced in 1995][9] and conditional marketing authorization [introduced in 2006][10] in the European Union).

We have recently shown the correlation between expedited regulatory approval programs offered by the FDA and the EMA, type of product (small molecule or biotechnology-derived product), or consulting scientific advisory committees and the regulatory review time of the MAAs for new anticancer drugs.[11] Here, a detailed analysis of the correlation among different expedited regulatory approval programs or type of product and the clinical development time of new anticancer drugs is presented.

METHODS

New anticancer drugs for which the Committee for Medicinal Products for Human Use (CHMP) of the EMA gave a positive opinion between January 2010 and December 2019 were identified by Garsen et al.[12] The

construction of the dataset composed of 76 new anticancer drugs with both positive CHMP opinion and FDA approval was recently described by da Costa Gonçalves et al.[11] The inclusion criteria were (i) article 8(3) full or full-mixed application as legal basis, (ii) new active substance, and (iii) products developed to treat cancer.[11,12] Information on the type of product (small molecule or biotechnology-derived product), expedited regulatory approval program (PRIME, accelerated assessment and conditional approval) in the European Union and clinical trial start date was extracted from the European Public Assessment Report (EPAR) and the summary of the CHMP opinion available on the EMA website. The dataset does not contain any drugs that underwent exceptional circumstances offered by the EMA.

Information on the date of submission of the MAA, date of approval of the drug by the FDA, type of MAA (new drug application [NDA] for small molecules and biologic license application [BLA] for biotechnology-derived products), expedited regulatory approval program (FTD, BTD, RMATD, and priority review and accelerated approval) in the United States and clinical trial start date was extracted from the FDA approval letters, administrative correspondence, and FDA application review files available in the Drugs@FDA database.

Different stages leading to marketing authorization and applicable expedited regulatory approval programs at each stage were defined as: (i) drug development (FTD, BTD, and RMATD in the United States, and PRIME in the European Union), (ii) review of MAA (priority review in the United States and accelerated assessment in the European Union), and (iii) approval of drug (accelerated approval in the United States and conditional approval in the European Union).[11] Each drug was classified to follow either a standard (i.e., no use of expedited regulatory approval programs at any stage) or an expedited regulatory approval pathway (i.e., use of at least one expedited regulatory approval program at least at one stage).

The databases ClinicalTrials.gov and the EU Clinical Trials Register were searched using the active ingredients of each drug as the search term. Search results from each database were filtered to display only early phase I and/or phase I studies, and were compared to select the earliest clinical trial start date. The clinical trial start date for an active ingredient was adjusted if an earlier date was encountered in an EPAR, FDA application review file (gemtuzumab ozogamicin [Clinical Review(s), Reference ID: 4138714, the first day of the month was selected due to lack of information]), or published manuscript (for alectinib,[13] dinutuximab[14] [the first day of the year of publication was selected due to lack of information], and trifluridine and tipiracil hydrochloride[15] [the first day of the year of publication was selected due to lack of information]). Clinical development time was calculated as the number of days that elapsed from the earliest clinical trial start date to the date of submission of the MAA in the United States (Table S1).

Box plots were created using the web tool BoxPlotR.[16]

RESULTS

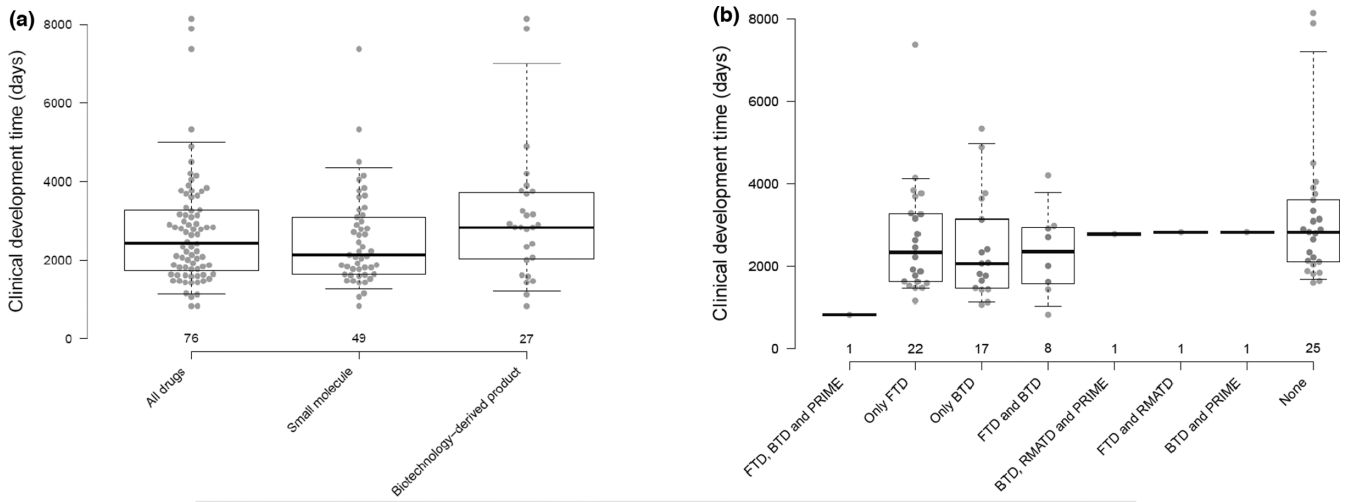
Clinical development time and type of product

The typical clinical development time of new anticancer drugs was 2432 days (6.7 years, $n = 76$). The type of product (i.e., small molecule or biotechnology-derived product), had a high impact on the clinical development time. The clinical development time of the small molecules was 2125 days (5.8 years, $n = 49$, [median]), whereas that of biotechnology-derived products was 2829 days (7.7 years, $n = 27$, [median]; Figure 1a).

Clinical development time and expedited regulatory approval programs at the drug development stage

Twenty-five drugs did not follow any expedited regulatory approval program at the drug development stage and the typical clinical development time of these drugs was 2829 days (7.7 years). In the United States, 51 drugs benefited from expedited regulatory approval programs at the drug development stage.[11] Thirty-two, 28, and two drugs underwent FTD, BTD, and RMATD, respectively. Drugs following only FTD and only BTD had a reduced clinical development time of 2335 days (6.4 years, $n = 22$, median) and 2061 days (5.6 years, $n = 17$, median), respectively. The clinical development time of eight drugs that followed both FTD and BTD was 2354 days (6.4 years, median). One biotechnology-derived product, namely talimogene, followed both FTD and RMATD leading to a clinical development time of 2826 days (7.7 years; Figure 1b).

In the European Union, only three drugs benefited from the expedited regulatory approval program PRIME at the drug development stage,[11] and these drugs also underwent FTD, BTD, and/or RMATD in the United States (Figure 1b). The time spent during the clinical development of these biotechnology-derived products, namely axicabtagene ciloleucel, polatuzumab vedotin-piiq, and tisagenlecleucel, was 820 days (2.2 years), 2829 days (7.7 years) and 2781 days (7.6 years), respectively (Figure 1b).



	Number of drugs	Clinical development time (days (median))
All drugs	76	2432
Type of product		
Small molecule	49	2125
Biotechnology-derived product	27	2829
Expedited regulatory approval programs followed at drug development stage		
FTD, BTD and PRIME	1	820
Only FTD	22	2335
Only BTD	17	2061
FTD and BTD	8	2354
BTD, RMATD and PRIME	1	2781
FTD and RMATD	1	2826
BTD and PRIME	1	2829
None	25	2829

FIGURE 1 Clinical development time and (a) type of product, and (b) expedited regulatory approval programs at the drug development stage. Data are presented as median and whiskers extending to 5th and 95th percentile. Number of data points is displayed on the x-axis for each category. BTD, breakthrough therapy designation; FTD, fast track designation; PRIME, priority medicines scheme; RMATD, regenerative medicine advanced therapy designation.

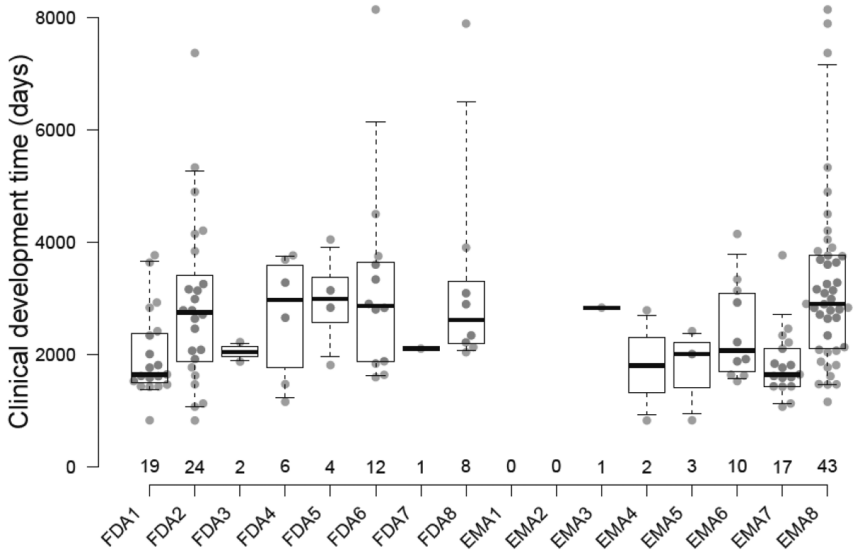
Clinical development time and expedited regulatory approval pathways

The clinical development time of new anticancer drugs following a standard (i.e., no use of expedited regulatory approval programs at any stage) or an expedited regulatory approval pathway (i.e., use of at least one expedited regulatory approval program at least at one stage; FDA1–FDA8 in the United States and EMA1–EMA8 in the European Union) were compared. In the United States, the clinical development time of new anticancer drugs undergoing at least one expedited regulatory approval program at the stage of drug development, priority review at the stage of review of MAA and accelerated approval at the stage of approval of drug was the shortest (FDA1, 1639 days [4.5 years, $n = 19$, median]), whereas that of drugs following the same regulatory pathway as FDA1 except accelerated approval (i.e., FDA2, 2744 days [7.5 years, $n = 24$, median]), was longer similar to that of those following the standard regulatory approval pathway (FDA8, 2612 days [7.2 years, $n = 8$, median]; Figure 2).

In the European Union, most of the new anticancer drugs did not follow PRIME at the stage of drug development ($n = 73$). The clinical development time of new anticancer drugs undergoing conditional approval at the stage of approval of drug without having used any expedited regulatory approval program at the stages of drug development and review of MAA (EMA7, 1639 days [4.5 years, $n = 17$, median]) was considerably shorter than that of those following the standard regulatory approval pathway (EMA8, 2826 days [7.7 years, $n = 43$, median]) or other pathways (including EMA6, 2064 days [5.7 years, $n = 10$, median]; Figure 2).

DISCUSSION

Considering that up to billions of dollars are spent during drug development, it is important for the



Regulatory approval pathway	Stages leading to marketing authorization			Number of drugs	Clinical development time (days (median))
	Drug development	Review of MAA	Approval of drug		
FDA1	FTD, BTD and/or RMATD	Priority review	Accelerated approval	19	1639
FDA2	FTD, BTD and/or RMATD	Priority review	Standard	24	2744
FDA3	FTD, BTD and/or RMATD	Standard	Accelerated approval	2	2042
FDA4	FTD, BTD and/or RMATD	Standard	Standard	6	2962
FDA5	Standard	Priority review	Accelerated approval	4	2983
FDA6	Standard	Priority review	Standard	12	2861
FDA7	Standard	Standard	Accelerated approval	1	2099
FDA8	Standard	Standard	Standard	8	2612
EMA1	PRIME	Accelerated assessment	Conditional approval	0	Not applicable
EMA2	PRIME	Accelerated assessment	Standard	0	Not applicable
EMA3	PRIME	Standard	Conditional approval	1	2829
EMA4	PRIME	Standard	Standard	2	1801
EMA5	Standard	Accelerated assessment	Conditional approval	3	2002
EMA6	Standard	Accelerated assessment	Standard	10	2064
EMA7	Standard	Standard	Conditional approval	17	1639
EMA8	Standard	Standard	Standard	43	2826

FIGURE 2 Clinical development time and expedited regulatory approval pathways. Data are presented as median and whiskers extending to 5th and 95th percentile. Number of data points is displayed on the x-axis for each category. BTD, breakthrough therapy designation; EMA, European Medicines Agency; FDA, US Food and Drug Administration; FTD, fast track designation; MAA, marketing authorization application; PRIME, priority medicines scheme; RMATD, regenerative medicine advanced therapy designation.

pharmaceutical industry to follow the best available regulatory strategy shortening the clinical development time and increasing the chance of regulatory approval. The regulatory agencies in the United States and the European Union, the FDA and the EMA, respectively, offer expedited regulatory approval programs for drugs with high potential patient value that expedite the development and review time of the MAA of such drugs. Drugs following FTD, BTD, RMATD, and PRIME are eligible for early and increased interaction and frequent meetings with the FDA and the EMA enabling continuous regulatory compliance and streamlining the development process,[17] whereas accelerated approval and conditional marketing authorization enable early approval supported by limited data before the confirmatory clinical studies are completed.[17] In this study, the correlation between different expedited regulatory approval programs or type of product (i.e., small molecule or biotechnology-derived product) and the clinical development time of 76 new anticancer drugs, with positive CHMP opinion between January 2010 and December 2019 and FDA approval, are analyzed.

We have previously shown that the date of submission of the MAAs for new anticancer drugs were comparable in the United States and the European Union, albeit mostly earlier in the United States.[11] In this study, clinical

development time was calculated as the number of days that elapsed from the earliest clinical trial (i.e., first-in-human study) start date to the date of submission of MAA in the United States (Table S1). In some cases, the earliest clinical trial start date extracted from public databases ClinicalTrials.gov and the EU Clinical Trials Register might not correspond with the actual first-in-human study on the corresponding active ingredient, considering the reportedly missing registration of trials in the databases, date of entry into force of the laws requiring registrations, and registrations of some types of trials not required by law (e.g., registration of some phase I clinical trials in the EU Clinical Trials Register).[18,19] It should also be noted that the clinical development time after the date of submission of the MAA in the United States (e.g., mandatory confirmatory clinical studies for the drugs approved via accelerated approval or conditional marketing authorization), was not included in the clinical development time in this study.

The typical clinical development time, calculated as the number of days that elapsed from the earliest clinical trial (i.e., first-in-human study) start date to the date of submission of the MAA in the United States, of new anticancer drugs was 6.7 years. Although the type of product did not have a high impact on the review time of the MAAs,[11] it had a high impact on the clinical development time (small molecules 5.8 years [median] vs. biotechnology-derived products 7.7 years [median]; Figure 1a).

Twenty-five drugs did not follow any expedited regulatory approval program at the drug development stage. Thirty-two, 28, three, and two drugs underwent FTD, BTD, PRIME, and RMATD, respectively, correlating with the duration these programs have been in effect (since 1987, 2012, 2016, and 2017, respectively). There are limited data on the effect of following PRIME and RMATD in clinical development time, and there is no drug in the dataset that followed only PRIME or only RMATD at the drug development stage. Drugs following only FTD, only BTD, and both FTD and BTD at the drug development stage had a reduced clinical development time of 6.4 years (median), 5.6 years (median), and 6.4 years (median), respectively, compared to drugs not following any expedited regulatory approval program at the drug development stage (7.7 years [median]). Drugs following only BTD typically had a shorter clinical development time than drugs following only FTD or both FTD and BTD (Figure 1b). These results are in line with a previously published analysis of clinical development time (from Investigational New Drug [IND] application to FDA approval between January 2012 and December 2016) of 174 new drugs: 7.1 years (interquartile range [IQR], 5.5–9.6) only FTD, 4.8 years (IQR, 3.6–8.3) only BTD, and 5.0 years (IQR, 2.9–7.7) both FTD and BTD.[20]

New anticancer drugs following expedited regulatory approval programs at the stages of drug development (FTD, BTD, and/or RMATD) and approval of drug (accelerated approval) in the United States (FDA1 and FDA3), and the new anticancer drugs following the standard procedure at the stage of drug development and an expedited regulatory approval program at the stage of approval of drug (conditional approval) in the European Union (EMA5 and EMA7) typically had a reduced clinical development time. These results confirm the strong correlation between undergoing BTD or accelerated approval in the United States and reduced clinical development time (from initiation of first in human clinical studies to FDA approval between 2010 and 2020) of 405 innovative drugs previously shown in another study.[21]

The regulatory pathways that correlated with the shortest clinical development time of 4.5 years (median) were FDA1 in the United States (at least one expedited regulatory approval program at the stage of drug development, priority review of the MAA, and approval of the drug) and EMA7 in the European Union (only conditional approval at the stage of approval of the drug; Figure 2). Although the clinical development time of drugs following these regulatory pathways are typically the same, the MAAs of the drugs following FDA1 were previously shown to have the shortest review time in the United States (172 days [median]), whereas the MAAs of the drugs following EMA7 were shown to have the longest review time in the European Union (392 days [median]).[11]

AUTHOR CONTRIBUTIONS

E.D., G.O., and A.Z. wrote the manuscript. A.Z. designed the research. E.D. and G.O. performed the research. E.D. and G.O. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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