

Oncology Drug Product Approvals and  
Postmarketing Requirements/Commitments in the  
Last Decade in the United States

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## **Abstract**

In the presence of malignant tumors, which are a typical representative of life-threatening diseases, sooner delivery of effective and safe oncology drug products to patients with cancer is imperative not only for pharmaceutical companies but also for regulatory agencies. Hence, there are some expedited programs for drug development and approval and those are applied for oncology drug products. The United States (US) has several expedited programs, such as Accelerated Approval (AA), Breakthrough Therapy (BT), Fast Track (FT), Priority Review (PR) and Orphan Drug (OD) Designation. Although several oncology drug products are receiving the designation of expedited programs, there are conflicting criticisms to the US Food and Drug Administration (FDA). Several previous studies investigated the characteristics of the approval of oncology drug products, but they were conducted with limited parameters or subjects, and no study has assessed AA, PR, and OD in combination.

Hence, study part I in this thesis aimed to investigate the relation between the expedited programs (AA, PR, and OD) and the characteristics of the oncology drug product approvals by expanding the investigation period and to evaluate FDA's attitude for the development and review of oncology drug products. As a result of investigation of 162 approvals during 2006-2016, it was shown that the proportion of OD is higher in AA compared with RA. On the contrary, no difference was observed in proportions of PR in AA versus RA or OD versus non-OD. In the comparison of development time, no difference was observed in AA versus RA, OD versus non-OD, or PR versus SR. Regarding the review time, no difference was observed in AA versus RA or OD versus non-OD; in contrast, a statistically significant difference was observed in PR versus SR.

In due course of accelerated drug development, some efficacy/safety issues are

bound to remain unresolved during the development stage; any of these concerns should be confirmed in the postmarketing setting. In the US, schemes to manage postmarketing studies, such as postmarketing requirement (PMR) and postmarketing commitment (PMC), have been implemented to validate the safety and efficacy of drug products after approval. Study part II aimed to investigate the characteristics of PMR/PMC for oncology drug products, assess factors that influence FDA decisions for PMR/PMCs during the FDA review of oncology drug products, and analyze FDA's attitude for the review of oncology drug products. As a result of investigation of 62 initial approvals and 279 PMR/PMCs, we identified that all approvals under AA required not only confirmatory PMR/PMC but also clinical safety PMR/ PMCs; however, only 41% required confirmatory PMR/PMCs, and 76% required clinical safety PMR/PMCs for RA. Also, the characteristics of pivotal studies, such as randomization, the number of patients, and endpoints, were identified as factors influencing the decisions about confirmatory and clinical safety PMR/PMCs.

The overall results of this research clarified the FDA's attitude on applying each expedited program for facilitating earlier delivery of drug products, and also the evaluation criteria for issues that remain unsolved until obtaining approval of drug products.

Based on these research findings, we would propose that pharmaceutical companies should take advantage of these expedited programs to deliver desired drug products to patients sooner, given the tremendous benefits of the programs for oncology product development. At the same time, companies should take any possible measures to avoid issues that remain unsolved after approval, especially safety issues, such as utilization of safety information from parallel development in multiple indications,

continuous efforts to improve the validation of surrogate endpoints, practical use of real-world data, and application of novel safety/efficacy predictor.

In the future, as the above measures become reality, we hope that many oncology drug products will be delivered to patients as early as possible along with necessary and sufficient safety/efficacy information at the time of launch.

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## Abbreviations

AA:	Accelerated Approval
BLA:	Biologic License Application
FDA:	the United States Food and Drug Administration
FDAAA:	FDA Amendments Act
FT:	Fast-Track Designation
IND:	Investigational New Drug
IQR:	Interquartile Range
NDA:	New Drug Application
NME:	New Molecular Entity
OD:	Orphan Drug Designation
PMC:	Postmarketing Commitment
PMR:	Postmarketing Requirement
RA:	Regular Approval
PDUFA:	Prescription Drug User Fee Act
PR:	Priority Review
SR:	Standard Review
US:	United States



## **1. Introduction**

Drug development is a convoluted and lengthy process marked by several stages in the drug discovery and development process that at times takes more than 10 years to launch a new molecular entity (NME) into the market (1). For patients with severe or life-threatening conditions with shorter survival span and no other treatment options, it is problematic to wait for drugs for a long time. Hence, the Food and Drug Administration (FDA) in the United States (US) has created expedited programs, such as Orphan Drug (OD) designation, Fast-Track (FT) designation, Breakthrough Therapy (BT) designation, Priority Review (PR), and Accelerated Approval (AA) (Table 1) (2).

The past few decades have witnessed a notable increase in the number of drugs approved under expedited programs in the US, especially oncology products. Kesselheim et al. (3) reported that , of the 107 oncology drugs approved between 1987 and 2014, 76% (81 of the 107 drugs) were approved with PR, 61% (65 of the 107 drugs) with OD, 48% (51 of the 107 drugs) with FT, and 30% (32 of the 107 drugs) with AA (3). Lately, the FDA has become more flexible in approving new drugs and has widely accepted the use of surrogate and intermediate endpoints rather than a clinical benefit endpoint, such as the overall survival (4), and has approved late-line therapies with single-arm trials in refractory populations (5). Other studies have revealed that the clinical trial to support the approval of orphan cancer drugs is more likely to be smaller and uses nonrandomized, unblinded trial designs and surrogate endpoints to assess the efficacy in comparison with non-orphan cancer drugs (6). Huang et al. (7) have suggested that the flexibility of the FDA has been consistent before and after the organizational change in the FDA (establishment of the Office of Oncology Drug Products) in 2005. Going by two opposing views, the FDA is too flexible in using

expedited programs, and the FDA poses hurdles in granting permission to expedited programs, there is an upsurge in both the controversy and criticism surrounding the FDA (8-14).

Previously, several studies have highlighted and demonstrated the flexibility of FDA in executing expedited programs; however, parameters considered in these studies were limited. Moreover, to date, no previous research has comprehensively investigated multiple combinations of available expedited programs such as AA, PR, and OD (5-7). Hence, the present research combines AA, PR, and OD as research parameters and expands the scope of the research period to the recent 10 years, and investigates FDA's flexibility in the development of oncology drug products.

Under expedited programs, many of oncology drug products developed are approved with surrogate endpoints and limited safety data to achieve earlier market access. In lieu of this, unresolved safety and efficacy issues persist throughout the development stage, which warrants confirmation after obtaining approval. Thus, accumulating data and evidence in the postmarketing setting have gained prominence. Jena et al. (15) identified the growing importance of postmarketing review and suggested an approach that would grant short-term access to novel drugs based on early evidence but would mandate long-term data from hard endpoints to continue the access.

Furthermore, the flexibility of the FDA is not only limited to approvals under expedited programs but has also expanded to traditional and regular approvals for products that are based on the seriousness of the disease and the availability of effective therapies as well as proven effects on surrogate or intermediate endpoints (16). Hence, the importance of postmarketing plans, including postmarketing requirements (PMRs) and postmarketing commitments (PMCs), has necessitated confirming the clinical

benefits of approved drugs.

The 2007 FDA Amendments Act (FDAAA) specifically authorized the FDA to mandate pharmaceutical companies to conduct PMR/PMCs (17). The FDA guidance provides several examples of PMRs, many of which are focused on safety evaluations of drug products, with some also conducted for efficacy evaluations along with safety.

As mentioned earlier, while some research studies have investigated the characteristics of products approved by the FDA under AA (5, 18), others have monitored and tracked PMR/PMCs by the FDA. However, to the best of our knowledge, no study has considered FDA's decision on PMR/PMCs. Hence, the present research investigates the characteristics of PMR/PMCs and factors that influenced FDA decisions for PMR/PMCs during the FDA review of oncology products.

Finally, based on the findings obtained in this research, we discuss the points of consideration when planning oncology drug development in the future.

**Table 1.** FDA Expedited Development and Review Programs

Program name	Year instituted	Characteristics of qualifying products	Does it formally change the evidentiary standard?	Phase during which it exerts most direct
Orphan Drug	1983	Treats disease occurring in <200,000 people per year in United States	No	Drug development
Fast Track	1988	Treats life-threatening or severely debilitating diseases	Yes; can approve after single phase 2 study	Drug development and FDA review
Priority Review	1992	Seems to offer therapeutic advance over available therapy	No	FDA review
Accelerated Approval	1992	Treats serious or life-threatening illnesses	Yes; can approve on the basis of surrogate endpoints reasonably likely to predict patient benefit	Drug development and FDA review
Breakthrough Therapy	2012	Treats serious disease for which preliminary clinical evidence suggests substantial improvement over existing therapies on one or more clinically essential endpoints	No	Drug development and FDA review

Adopted from Kesselheim et al. (3)

## **2. Part I**

### **2.1. Part I: Objectives**

Recently, several oncology drug products have received the designation of expedited programs, including AA, PR, or OD, in the US. Owing to some criticism surrounding the FDA regarding the utilization of these expedited programs, several previous studies have investigated the characteristics of the approval of oncology drug products receiving the designation of AA or OD and have supported the FDA's high flexibility in this regard (5-7). However, these investigations have been conducted with limited parameters or subjects (e.g., development time and/or the characteristics of pivotal study); no study has comprehensively analyzed multiple combinations of available expedited programs such as AA, PR, and OD.

Therefore, the objectives of this study were to analyze the relation between the expedited programs such as AA, PR, and OD and the characteristics of the oncology drug product approvals by expanding the period of subject to recent 10 years (2006-2016), and to assess FDA's attitude for accelerating the development and review of oncology drug products.

### **2.2. Part I: Methods**

On its website, the FDA issues Hematology/Oncology (Cancer) Approvals and Safety Notifications and publishes approval letters and summary reports on the basis of approval (19, 20). From these documents, we first prepared a list of approvals of oncology drug products, including initial approvals for NMEs and supplemental approvals for additional indications. Then, we collected information about the characteristics of oncology drug products for their approvals, including product name, submission date, approval date, type of approval, indication, drug class, type of pivotal

study, endpoint for the pivotal study, and number of patients in the pivotal study. The duration of the review (days between submission date and approval date) was also calculated. Moreover, dates, when the initial investigational new drug (IND) application became effective, were collected from any of the two sources, the publication of patent extension in the Federal Register or documents available in New Drug Application (NDA)/Biologic License Application (BLA) review reports (such as Medical Review Report). After that, we calculated the duration of the total drug development (years between the date when the initial IND became effective and the date of market approval) for initial approvals. In approvals for additional indications, as IND effective date for its indication could not be identified, the duration of the total drug development was not calculated.

For our evaluation, we first analyzed the characteristics of approvals ( $n = 162$ ) within the investigational period (2006-2016) for the type of approvals (initial/supplemental, NDA/BLA), type of expedited programs (AA, OD, and PR), review time, and characteristics of the pivotal study (i.e., randomization, numbers of patients, and primary endpoint). Second, we analyzed the characteristics of products with or without expedited programs, such as AA versus regular approval (RA), OD versus non-OD, and PR versus standard review (SR). Third, we analyzed changes in the characteristics of approval and pivotal study year by year.

We used R (version 3.4.2) and R studio (ver. 1.1.383) for all the calculations and statistical analyses. The Wilcoxon rank-sum test was used to compare continuous variables, and the Fisher's exact test was applied to categorical variables.

## **2.3. Part I: Results**

### **2.3.1. Oncology Drug Product Approvals from 2006 to 2016**

We included 162 approvals in this analysis (Table 2), of which 71 (44%) were initial approvals for NMEs and 91 (56%) were supplemental approvals for additional indications. While two-thirds (106 of the 162) received NDA approvals, one-third (56 of the 162) received BLA approvals. Of 162 products, 89 were approved with indications for OD, and 73 were approved for non-OD indications. Furthermore, three-quarters received approvals under PR, and one-quarter received approvals under the SR. The median duration of the review was 183 days (interquartile range [IQR], 168-274 days). In pivotal studies for approval of the products, 114 were randomized. The median number of patients in pivotal studies was 396 (IQR, 173-673 patients). Moreover, one-quarter were approved based on the pivotal study with OS as the primary endpoint, and third-quarter were approved with primary endpoints other than OS such as the progression or response rate.

**Table 2.** Summary of Findings and Characteristics of Oncology Drug Products  
Approved from 2006 to 2016

		Approvals 2006-2016 ( <i>n</i> = 162)	
Approvals			
Initial Approval			
	Initial approval, <i>n</i> (%)	71	(44)
	Supplemental approval, <i>n</i> (%)	91	(56)
NDA/BLA			
	NDA, <i>n</i> (%)	106	(65)
	BLA, <i>n</i> (%)	56	(35)
Accelerated Approval			
	AA, <i>n</i> (%)	46	(28)
	RA, <i>n</i> (%)	116	(72)
Orphan Drug			
	OD, <i>n</i> (%)	89	(55)
	Non-OD, <i>n</i> (%)	73	(45)
Priority Review*			
	PR, <i>n</i> (%)	119	(76)
	SR, <i>n</i> (%)	37	(24)
Review Time, in days, median [IQR]		183	[168-274]
Pivotal Study			
RCT			
	Randomized, <i>n</i> (%)	114	(70)
	Nonrandomized, <i>n</i> (%)	48	(30)
No. of patients, median [IQR]		396	[173-673]
Primary endpoint			
	OS, <i>n</i> (%)	44	(27)
	Progression, <i>n</i> (%)	56	(35)
	Response rate, <i>n</i> (%)	61	(38)
	Other, <i>n</i> (%)	1	(1)

\**n* = 156 due to NA data



### 2.3.2. Combined Analysis of Expedited Programs

Table 3 summarizes the results of the analysis of multiple combinations of expedited programs, AA, OD, and PR. In the comparison between AA and RA, the proportion of OD is higher in AA compared with RA (70% vs. 49%;  $P = 0.023$ ). On the contrary, no difference was observed in proportions of PR between AA and RA (80% vs. 75%;  $P = 0.540$ ) or OD and non-OD (74% vs. 79%;  $P = 0.576$ ).

**Table 3.** Combined Analysis of Expedited Programs

	Accelerated Approval		$P^{\#}$	Orphan Drug		$P^{\#}$
	AA	RA		OD	Non-OD	
Orphan Drug	( $n = 46$ )	( $n = 116$ )				
OD, $n$ (%)	32 (70)	57 (49)				
Non-OD, $n$ (%)	14 (30)	59 (51)	0.023			
Priority Review*	( $n = 45$ )	( $n = 111$ )		( $n = 86$ )	( $n = 70$ )	
PR, $n$ (%)	36 (80)	83 (75)		64 (74)	55 (79)	
SR, $n$ (%)	9 (20)	28 (25)	0.540	22 (26)	15 (21)	0.576

AA, accelerated approval; RA, regular approval; OD, orphan drug designation; Non-OD, non-orphan drug designation; PR, priority review; SR, standard review

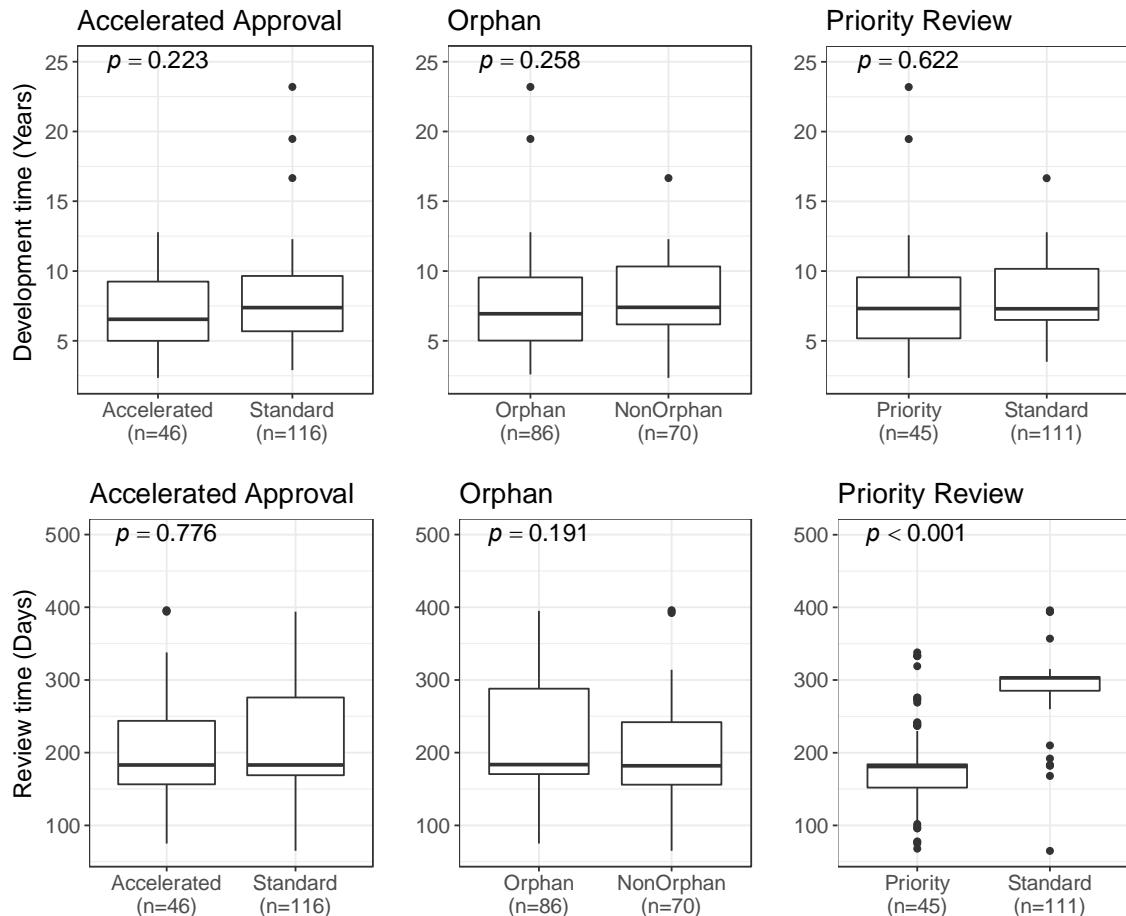
\* $n = 156$  due to NA data

#Fisher's exact test

Regarding the development time in 71 initial approvals, no difference was observed between AA (6.55 years; IQR: 5.00-6.92) and RA (7.38 years; IQR: 5.68-6.65;  $P = 0.233$ ); OD (6.94 years; IQR: 5.02-6.95) and non-OD (7.40 years; IQR: 6.18-10.33;  $P = 0.258$ ); and PR (7.32 years; IQR: 5.18-6.95) and SR (7.30 years; IQR: 6.56-10.16;  $P = 0.622$ ). Regarding the review time in all approvals ( $n = 162$ ), no difference was observed between AA (183 days; IQR: 157-244) and RA (183 days; IQR: 169-276;  $P = 0.776$ ) and OD (184 days; IQR: 171-288) and non-OD (182 days; IQR: 157-256;  $P = 0.191$ ). In contrast, a statistically significant difference was observed between PR and SR. The review time in PR was 180 days (IQR: 153-184) that was statistically

shorter than that in SR (303 days; IRQ: 2836304;  $P < 0.001$ ; Figure 1).

**Figure 1.** Comparison between the Development Time and the Review Time



$P$  values: Wilcoxon Rank-Sum Test

### 2.3.3. Characteristics of Pivotal Studies

We investigated the characteristics of the pivotal study by comparing the pivotal study for products approved with and without expedited program designation (Table 4). In comparison between AA and RA (Table 4a), the proportion of products approved under AA with a randomized pivotal study was significantly less than those with a nonrandomized pivotal study ( $P < 0.001$ ). For products approved under AA, the number of patients in the pivotal study was less than that for products under RA

( $P < 0.001$ ). In the analysis of primary endpoint in the pivotal study, the proportion of products approved under AA was higher for products approved with the response rate as a primary endpoint than those with the progression rate or OS.

In comparison between OD and non-OD (Table 4b), the proportion of products under OD with a randomized pivotal study was significantly less for those with a nonrandomized pivotal study ( $P < 0.001$ ). For products approved under OD, the number of patients in the pivotal study was less than that under non-OD ( $P < 0.001$ ). In the analysis of the primary endpoint in the pivotal study, the proportion of products approved under OD was higher for products approved with the response rate as a primary endpoint than those with the progression rate or OS. We observed no significant difference in parameters investigated in PR and SR (Table 4c).

**Table 4.** Characteristics of the Pivotal Study with or without Expedite Programs**a. Accelerated Approval**

	AA	RA	<i>P</i> <sup>#</sup>
Randomization			
RCT, <i>n</i> (%) ( <i>n</i> = 114)	19 (17)	95 (83)	<0.001
Non-RCT, <i>n</i> (%) ( <i>n</i> = 48)	27 (56)	21 (44)	
No. of patients, median [IQR]	[1176 169 330]	[3176 458 731]	<0.001
Primary endpoint			
OS, <i>n</i> (%) ( <i>n</i> = 44)	3 (7)	41 (93)	<0.001
Progression, <i>n</i> (%) ( <i>n</i> = 56)	7 (13)	49 (88)	
Response rate, <i>n</i> (%) ( <i>n</i> = 61)	36 (59)	25 (41)	
Other, <i>n</i> (%) ( <i>n</i> = 1)	0 (0)	1 (100)	

**b. Orphan Drug Designation**

	OD	Non-OD	<i>P</i> <sup>#</sup>
Randomization			
RCT, <i>n</i> (%) ( <i>n</i> = 114)	50 (44)	64 (56)	<0.001
Non-RCT, <i>n</i> (%) ( <i>n</i> = 48)	39 (81)	9 (19)	
No. of patients, median [IQR]	[1346 263 474]	[3566 572 829]	<0.001
Primary endpoint, <i>n</i> (%)			
OS, <i>n</i> (%) ( <i>n</i> = 44)	14 (32)	30 (68)	<0.001
Progression, <i>n</i> (%) ( <i>n</i> = 56)	28 (50)	28 (50)	
Response rate, <i>n</i> (%) ( <i>n</i> = 61)	46 (75)	15 (25)	
Other, <i>n</i> (%) ( <i>n</i> = 1)	1 (100)	0 (0)	

**c. Priority Review**

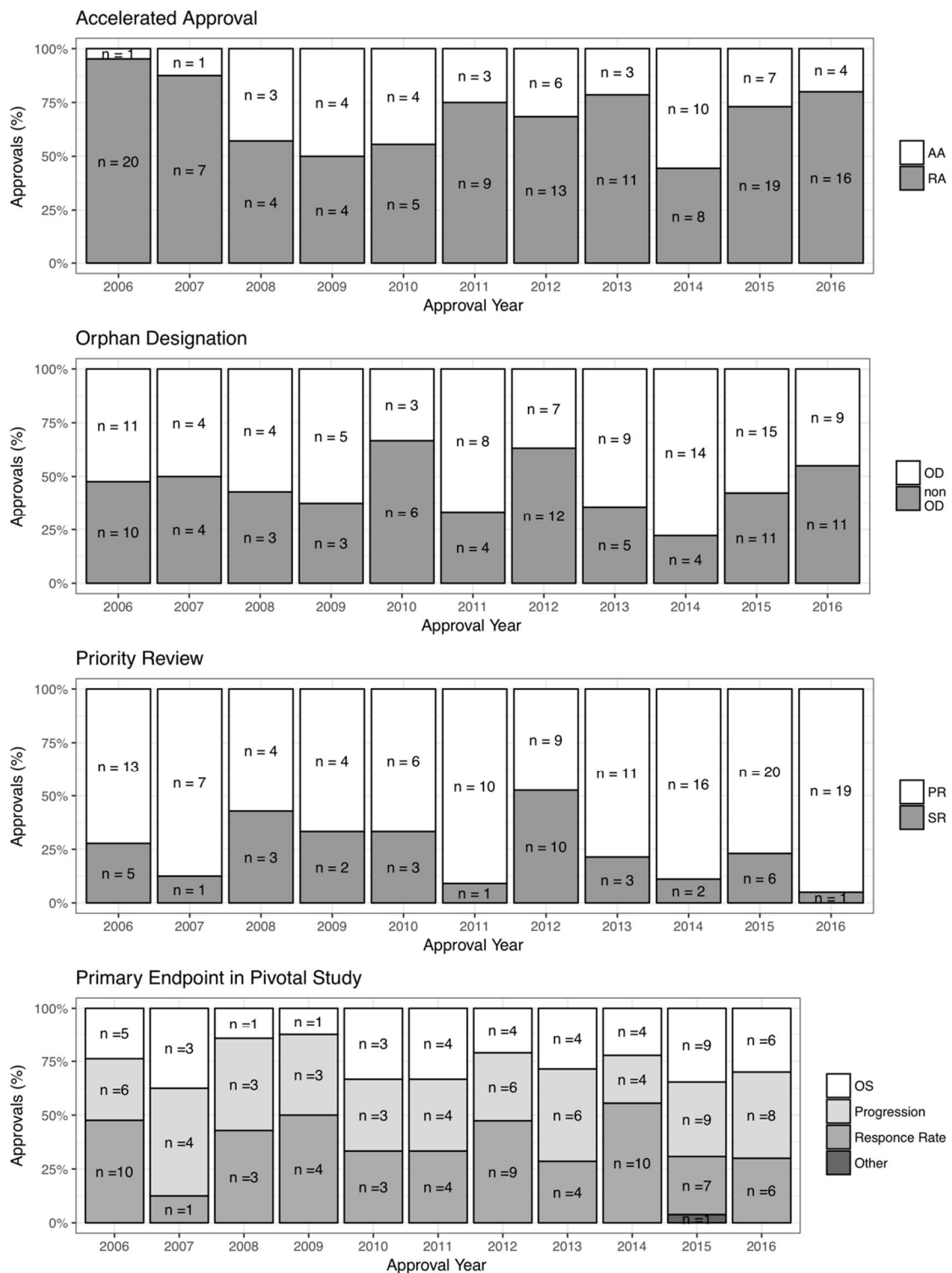
	PR	SR	<i>P</i> <sup>#</sup>
Randomization			
RCT, <i>n</i> (%) ( <i>n</i> = 114)	85 (77)	25 (23)	0.682
Non-RCT, <i>n</i> (%) ( <i>n</i> = 48)	34 (74)	12 (26)	
No. of patients, median [IQR]	[1746 392 646]	[1706 463 800]	0.513
Primary endpoint, <i>n</i> (%)			
OS, <i>n</i> (%) ( <i>n</i> = 44)	35 (81)	8 (19)	0.211
Progression, <i>n</i> (%) ( <i>n</i> = 56)	42 (79)	11 (21)	
Response rate, <i>n</i> (%) ( <i>n</i> = 61)	42 (71)	17 (29)	
Other, <i>n</i> (%) ( <i>n</i> = 1)	0 (0)	1 (100)	

<sup>#</sup>Wilcoxon rank-sum tests were for continuous variables, and the Fisher's exact test was for categorical variables.

#### **2.3.4. Time-course changes in the characteristics of approvals**

In this study, we investigated the time-course changes in the characteristics of approvals (AA, OD, and PR) and the primary endpoint in the pivotal study (Figure 2). In AA, the proportion of AA was smaller in 2006 and 2007 compared with the following years; however, no apparent tendency of increase or decrease was noted in the proportion of AA. In OD, no trend of change was observed in the proportion of OD for 10 years. In PR, no clear trend of changes was observed. In the investigation of the primary endpoint of the pivotal study, no trend was noted in the proportion of OS and other endpoints.

**Figure 2. Time-Course Changes in the Characteristics of Approvals**



## **2.4. Part I: Discussion**

In comparison with the statistically significant difference observed in the proportion of OD in AA and RA, no difference was observed in the proportion of PR in AA versus RA and OD versus non-OD, which were approximately 80% (Table 3). This novel result obtained by comparing the multiple expedited programs suggests no relation between the expedited programs aimed at accelerating the drug development, such as AA and OD, and the expedited programs aimed at accelerating the review time of drug product, namely PR.

Moreover, we observed no difference in the review time between AA versus RA and OD versus non-OD. In contrast, the review time in PR was statistically shorter than that in SR (Figure 1). These results suggested that the FDA designates PR to products that fulfill the PR criteria, seemingly offering a therapeutic advantage over the available therapy, even if it is an RA or non-OD product. Furthermore, the FDA accelerates the review based on the PR program to meet the Prescription Drug User Fee Act (PDUFA) review time goal, 180 days (21). In other words, even if the product is designated AA or OD to accelerate the development, if it does not meet the PR criteria, the FDA reviews it under SR that takes 10-month review time per PDUFA review time standard goal.

Although the AA provision was instituted to facilitate the earlier approval of drugs or biologics that treat acute conditions (22, 23), no difference was observed in the development time for products approved by AA compared with those approved by RA (Figure 1), which corroborated the result of a previous research for oncology drugs approved in the US between 1995 and 2008 (Richey et al. (24)). In response to Richey et al., Lanthier et al. (18) highlighted that AA allows the use of surrogate endpoints in the registration trial, which can only influence the time to complete the trial itself.

Furthermore, they suggested that the development time is convoluted and might be affected by factors other than the time to complete the registration trial. Our results indicate that the FDA has approved products by AA with nonrandomized smaller studies that evaluate response rates (Table 4), which, perhaps, implies that if these products had not been developed under AA, larger and longer registration studies would have been mandatory and, consequently, a more prolonged development period would have followed. Hence, it could be considered that the AA provision has shortened the product development period to the level of RA. Moreover, this study suggests the occurrence of a similar situation in products under OD.

Furthermore, the time-course analysis of the characteristics of approvals suggested that FDA's flexibility for oncology drug products has remained unchanged over time and is comparable with the characteristics reported in previous studies.

Nonetheless, the FDA has allegedly compromised its standards in its rush to approve new drugs on the basis of surrogate endpoints (8614). This research demonstrates that the FDA is contributing to the acceleration of oncology drug development and review in expedited programs. In other words, the FDA is contributing to delivering innovative oncology drug products sooner to patients.



### **3. Part II: Factors that Affect FDA Decisions for Postmarketing Requirements and Commitments during Review of Oncology Products**

#### **3.1. Part II: Objectives**

The part I of this research revealed that FDA's flexibility for oncology drug products has remained unchanged, and the FDA is utilizing expedited programs to contribute delivering earlier patients' access to innovative oncology drug products.

However, expedited programs could increase some safety and/or efficacy issues that are most likely to remain unsolved. Precisely, under FDA's current situation that allows the acceleration of drug development, oncology drug products tend to be developed with a shorter development time and smaller and less robust pivotal studies. Hence, some type of safety and/or efficacy issues, those which in case of standard approval warrant a solution before launching, persist and could be regarded as postmarketing issues.

Accordingly, this part of the study focused on factors that affect the FDA's decision regarding PMR/PMCs or, in other words, factors that affect the FDA's judgment about unsolved efficacy/safety issues at the development stage. To the best of our knowledge, no study has investigated the FDA's decision on PMR/PMCs. We believe that this is the first study to investigate the characteristics of PMR/PMCs with or without expedited programs and to assess factors that affected the FDA decisions for PMR/PMCs during the FDA review of oncology products.

#### **3.2. Part II: Methods**

To evaluate PMR/PMCs, we set the investigational period between 2008 and 2016 (8 years), as the new authority for postmarketing clinical studies/trials became effective on March 25, 2008. On September 27, 2007, the President of the United States of America signed the FDAAA of 2007 (Public Law 110-85), wherein Section 901, in Title

IX of FDAAA, created section 505(o) of the Federal Food, Drug, and Cosmetic Act (the Act), which authorized the FDA to mandate certain studies and clinical trials for prescription drugs and biological products approved under section 505 of the Act or Section 351 of the Public Health Service Act. This new authority became effective on March 25, 2008.

Moreover, we focused on initial approvals for NMEs because we considered that the inclusion of approvals for additional indication might affect the evaluation of PMR/PMC decisions. Accordingly, we collected the information about PMR/PMCs for approved drugs from their approval letters published on the FDA's website (20). Since there are variety types of PMR/PMCs, we categorized PMR/PMCs according to different criteria (Table 5), such as the study objective, study conduct, and authorization. Based on the type of study objective, PMR/PMCs were categorized into four as follows: (a) "confirmatory", PMR/PMCs that included clinical studies indicated as phase III, confirmatory, or equivalent (e.g., randomized study to demonstrate the efficacy and safety) ; (b) "clinical safety", PMR/PMCs that contained clinical studies or any safety evaluation other than a confirmatory study, such as phase I, I/II, or II, or other safety studies; (c) "clinical pharmacology", PMR/PMCs with studies of drug-drug interactions, pharmacokinetics with special populations, or food effect studies; and (d) "others", PMR/PMCs with other studies, such as nonclinical or pharmaceutical quality-related studies. According to the type of study conduct, PMR/PMCs were categorized into the following two categories: (a) conduct of a new study or (b) follow-up for an existing study. Based on the type of authorization and regulatory categories, PMR/PMCs were categorized into the following two categories: (a) PMR under subpart H (22), under subpart E (23), or under section 505(o) of the Federal Food, Drug, and Cosmetic Act

(21 U.S.C. 355[o]) or (b) PMC under section 506B of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356b).

Furthermore, PMR/PMCs were scored on the basis of the definition and criteria described in Table 5 to generate a weighted score for PMR/PMCs. For example, confirmatory study scored 3 because it requires more burden and has a greater significance than other studies. Moreover, scores for individual PMR/PMC (PMR/PMC score) were calculated by multiplying the scores for each category. For example, PMR/PMC score for a PMR (score 2) that required conduct (score 2) of a confirmatory study (score 3) would be given a score of 12. After that, we calculated scores of each product by summing the PMR/PMC scores of all PMR/PMCs (Product score). The validity of these scoring criteria was confirmed with a sensitivity analysis with varying scoring criteria.

For the evaluation, we first analyzed the characteristics of products approved within the investigational period ( $n = 62$  products) for the type of approvals (NDA/BLA), type of expedited programs (AA, OD, and PR), review time, development time, characteristics of pivotal study (randomization, numbers of patients, and primary endpoint), and PMR/PMCs required (number and types of PMR/PMCs and Product score for PMR/PMCs). Moreover, the characteristics of PMR/PMCs were summarized. Second, we analyzed the characteristics of PMR/PMCs with or without expedited programs, such as AA versus RA, OD versus non-OD, and PR versus SR. Third, we analyzed the characteristics of products with or without PMR/PMCs for studies categorized as confirmatory clinical studies (confirmatory PMR/PMCs), clinical safety studies (clinical safety PMR/PMCs), or clinical pharmacology studies (clinical pharmacology PMR/PMCs).

We used R (version 3.4.2) and R studio (ver. 1.1.383) for all calculations and statistical analyses. The Wilcoxon rank-sum test was used to compare continuous variables, and the Fisher's exact test was applied to categorical variables.

**Table 5.** PMR/PMC Categories and Scores for Evaluation

Category		Score
Type of Study by Objective	Confirmatory Study	3
	Clinical Safety Study	2
	Clinical Pharmacology Study: Drug-drug interaction, Study in Special Population, Food Effect Study, etc.	1
	Others: Nonclinical Study, CMC-related study, etc.	1
Type of Study by Study Conduct	Conduct New Study	2
	Follow-up for Existing Study	1
Type of PMR/PMC	PMR	2
	PMC	1

## Part II: Results

### 3.2.1. Characteristics of Products and PMR/PMCs

We included 62 products in this analysis (Table 6), of which 44 received NDA approvals, and 18 received BLA approvals. Overall, 25 products were approved under the AA process; of which, 11 were converted to RA after the completion of confirmatory trials, and the remaining 14 were yet to complete confirmatory trials at the time of this research (ongoing, pending, or delayed). Of 62 products, 21 were approved with indications designated as an orphan, and 41 were approved without a designation for the orphan. The median duration of review and drug development were 172 days (IQR: 156-194 days) and 7.5 years (IQR: 5.3-10.1 years), respectively. In pivotal studies for the approval of products, 39 studies were randomized. The median number of patients in pivotal studies was 331 (IQR: 169-602 patients). The median number of PMR/PMCs

per product was 4.0 (IQR: 2.0-6.0 PMR/PMCs). Among 62 products, confirmatory studies were required for and/or committed to 40 products, clinical safety studies for 53 products, and clinical pharmacology studies for 33 products. Only 4 of the 62 products required neither PMRs nor PMCs. The median product score for PMR/PMCs was 22 (IQR: 11-40).

In this study, the total number of PMR/PMCs was 279 for 62 products, of which 59 PMR/PMCs were categorized as confirmatory PMR/PMCs for 40 products. The numbers of PMR/PMCs that required a study or follow-up of an existing study were 142 and 137, respectively. The number of PMR/PMCs under subparts H/E was 43 and under 505(o) was 193 (Table 7).

**Table 6.** Characteristics of the Products and PMR/PMCs

		Initial Approvals 2008-2016 ( <i>n</i> = 62)	
Approval			
NDA/BLA			
	NDA, <i>n</i> (%)	44	(71)
	BLA, <i>n</i> (%)	18	(29)
Accelerated			
	AA, <i>n</i> (%)	25	(40)
	RA, <i>n</i> (%)	37	(60)
Orphan			
	OD, <i>n</i> (%)	21	(34)
	Non-OD, <i>n</i> (%)	41	(66)
Priority Review*			
	PR	47	(77)
	SR	14	(23)
Review time, in days, median [IQR]		172	[156-194]
Development time, in years, median [IQR]		7.4	[5.3-10.1]
Pivotal Study			
RCT			
	Randomized, <i>n</i> (%)	39	(63)
	Nonrandomized, <i>n</i> (%)	23	(37)
No. of patients, median [IQR]		331	[169-602]
Primary endpoint			
	OS, <i>n</i> (%)	16	(26)
	Progression, <i>n</i> (%)	17	(27)
	Response rate, <i>n</i> (%)	29	(47)
PMR/PMCs			
Number of PMR/PMCs per NDA/BLA, median [IQR]		4.0	[2.0-6.0]
Confirmatory study PMR/PMCs			
	With PMR/PMCs, <i>n</i> (%)	40	(65)
	Without PMR/PMCs, <i>n</i> (%)	22	(35)
Clinical safety PMR/PMCs			
	With PMR/PMCs, <i>n</i> (%)	53	(85)
	Without PMR/PMCs, <i>n</i> (%)	9	(15)
Clinical pharmacology PMR/PMCs			
	With PMR/PMCs, <i>n</i> (%)	33	(53)
	Without PMR/PMCs, <i>n</i> (%)	29	(47)
Product score for PMR/PMC, median [IQR]		22	[11-40]

**Table 6.** Summary of PMR/PMCs

	PMR/PMC ( <i>n</i> = 279)
Type of Study by Objective	
Confirmatory study	59 (21)
Clinical safety study	73 (26)
Clinical pharmacology study	90 (32)
Other study	57 (20)
Type of Study by Study Conduct	
Conduct new study	142 (51)
Follow-up for existing study	137 (49)
Type of PMR/PMC	
PMR under subpart H/E	43 (15)
PMR under 505(o)	193 (69)
PMC under 506 (b)	43 (15)

### 3.2.2. Characteristics of PMR/PMC

Of 62 products, 25 were approved under AA, and 37 were approved under RA (Tables 8a). The median numbers of PMR/PMCs required under AA and RA were 5.0 (IQR: 3.0-7.0) and 3.0 (IQR: 2.0-6.0), respectively. Although this number was slightly higher for AA, it was not statistically significant ( $P = 0.103$ ). All approvals under AA required confirmatory and/or clinical safety PMR/PMCs. In contrast, regarding RA, only 41% required confirmatory PMR/PMCs, and 76% required clinical safety PMR/PMCs ( $P < 0.001$  and  $P = 0.008$ , respectively, compared with AA). Irrespective of a product's approval by AA or RA, approximately 50% of products required clinical pharmacology PMR/PMCs. The median product score for PMR/PMC under AA (33; IQR: 18-54) was higher than that under RA (20; IQR: 8-28;  $P = 0.001$ ).

As for the comparison between OOD and non-OD and PR and SR, no significant difference was observed in parameters investigated for the characteristics of PMR/PMCs (Table 8b and 8c).

**Table 7.** Characteristics of PMR/PMCs**a. Accelerated Approval**

	AA ( <i>n</i> = 25)	RA ( <i>n</i> = 37)	<i>P</i> <sup>#</sup>
Number of PMR/PMCs, median [IQR]	5.0 [3.067.0]	3.0 [2.066.0]	0.103
Confirmatory study PMR/PMCs			
Products with PMR/PMCs, <i>n</i> (%)	25 (100)	15 (41)	
Products without PMR/PMCs, <i>n</i> (%)	0 (0)	22 (59)	<0.001
Clinical safety PMR/PMCs			
Products with PMR/PMCs, <i>n</i> (%)	25 (100)	28 (76)	
Products without PMR/PMCs, <i>n</i> (%)	0 (0)	9 (24)	0.008
Clinical pharmacology PMR/PMCs			
Products with PMR/PMCs, <i>n</i> (%)	12 (48)	21 (57)	
Products without PMR/PMCs, <i>n</i> (%)	13 (52)	16 (43)	0.606
Product score for PMR/PMC, median [IQR]	33 [18654]	20 [8628]	0.001

**b. Orphan Drug Designation**

	OD ( <i>n</i> = 41)	Non-OD ( <i>n</i> = 21)	<i>P</i> <sup>#</sup>
Number of PMR/PMCs, median [IQR]	4.0 [2.067.0]	4.0 [3.066.0]	0.988
Confirmatory study PMR/PMCs			
Products with PMR/PMCs, <i>n</i> (%)	30 (73)	10 (48)	
Products without PMR/PMCs, <i>n</i> (%)	11 (27)	11 (52)	0.056
Clinical safety PMR/PMCs			
Products with PMR/PMCs, <i>n</i> (%)	37 (90)	16 (76)	
Products without PMR/PMCs, <i>n</i> (%)	4 (10)	5 (24)	0.251
Clinical pharmacology PMR/PMCs			
Products with PMR/PMCs, <i>n</i> (%)	20 (49)	13 (62)	
Products without PMR/PMCs, <i>n</i> (%)	21 (51)	8 (38)	0.423
Product score for PMR/PMC, median [IQR]	22 [10644]	20 [13628]	0.571

**c. Priority Review**

	PR ( <i>n</i> = 25)	SR ( <i>n</i> = 37)	<i>P</i> <sup>#</sup>
Number of PMR/PMCs, median [IQR]	4 [2.066.0]	3.5 [2.067.8]	0.959
Confirmatory study PMR/PMCs			
Products with PMR/PMCs, <i>n</i> (%)	33 (70)	6 (43)	
Products without PMR/PMCs, <i>n</i> (%)	14 (30)	8 (57)	0.111
Clinical safety PMR/PMCs			
Products with PMR/PMCs, <i>n</i> (%)	41 (87)	11 (79)	
Products without PMR/PMCs, <i>n</i> (%)	6 (13)	3 (21)	0.416
Clinical pharmacology PMR/PMCs			
Products with PMR/PMCs, <i>n</i> (%)	23 (49)	9 (64)	
Products without PMR/PMCs, <i>n</i> (%)	24 (51)	5 (36)	0.372
Product score for PMR/PMC, median [IQR]	22 [11632]	20 [9647]	0.877

<sup>#</sup>Wilcoxon rank-sum test was for continuous variables, and the Fisher's exact test was for categorical variables.



### **3.2.3. Characteristics of Pivotal Study in Products Approved with or without Confirmatory/Clinical Safety/Clinical Pharmacology PMR/PMCs**

We investigated the features of products by comparing the proportion of products with and without confirmatory PMR/PMCs (Table 9). The proportion of products with confirmatory PMR/PMCs was significantly less for products with a randomized pivotal study than for those with a nonrandomized pivotal study ( $P < 0.001$ ). For products approved with confirmatory PMR/PMCs, the number of patients in the pivotal studies was less than that for products without confirmatory PMR/PMCs ( $P = 0.006$ ). For a majority of products approved on the basis of the response rate as the primary endpoint, confirmatory PMR/PMCs were required ( $P = 0.009$ ).

Furthermore, we investigated the characteristics of products approved with clinical safety PMR/PMCs by comparing the proportion of products with clinical safety PMR/PMCs (Table 9). The percentage of products approved with clinical safety PMR/PMCs was significantly less for products with a randomized pivotal study than for those with a nonrandomized pivotal study ( $P = 0.020$ ). For products approved with clinical safety PMR/PMCs, the number of patients in pivotal studies was less than that for products without clinical safety PMR/PMCs ( $P < 0.001$ ). For all the products approved on the basis of the response rate as the primary endpoint, clinical safety PMR/PMCs were required ( $P < 0.001$ ). We noted no significant difference in parameters investigated for clinical pharmacology PMR/PMCs (data are not shown).

**Table 8.** Characteristics of the Pivotal Study in Products Approved with or without Confirmatory/Clinical Safety PMR/PMC

	Confirmatory PMR/PMCs		<i>P</i> <sup>#</sup>	Clinical Safety PMR/PMCs		<i>P</i> <sup>#</sup>
	Yes	No		Yes	No	
Randomization						
RCT, <i>n</i> (%) ( <i>n</i> = 39)	19 (49)	20 (51)		30 (77)	9 (23)	
Non-RCT, <i>n</i> (%) ( <i>n</i> = 23)	21 (91)	2 (9)	< 0.001	23 (100)	0 (0)	0.020
No. of patients, median [IQR]	[1506 248 439]	[2686 530 790]	0.006	[1636 255 495]	[7226 800 1093]	<0.001
Primary endpoint						
OS, <i>n</i> (%) ( <i>n</i> = 15)	5 (33)	10 (67)		10 (63)	6 (38)	
Progression, <i>n</i> (%) ( <i>n</i> = 17)	10 (59)	7 (41)		14 (82)	3 (18)	
Response rate, <i>n</i> (%) ( <i>n</i> = 29)	24 (83)	5 (17)	0.009	29 (100)	0 (0)	<0.001

<sup>#</sup>Wilcoxon rank-sum tests were for continuous variables, and the Fisher's exact test was for categorical variables.

### **3.3. Part II: Discussion**

As the safety and efficacy questions remain unanswered at the time of approval, these warrant an answer in the postmarketing period as PMR/PMCs. Regarding AA, in particular, the confirmation of efficacy should be mandated after approval as PMR because of the characteristics of the program evaluating the efficacy of a drug product based on surrogate endpoints. Therefore, we anticipated that more PMR/PMCs would be required for products marketed under AA than for those marketed under RA. However, the median number of PMR/PMCs under AA was only slightly higher than that under RA, and the difference was not statistically significant (Table 8a). Based on these results, we considered that weight and/or significance of PMR/PMCs could be more important than the number of PMR/PMCs. In fact, the results of the categorization of PMR/PMCs suggested the presence of various PMR/PMCs with varied weights and/or significances among PMR/PMCs required for the approval of drug products (Table 7). Furthermore, the PMR/PMC score was higher in products under AA than that under RA. Moreover, while all approvals under AA required not only confirmatory PMR/PMC but also clinical safety PMR/ PMCs, only 41% required confirmatory PMR/PMCs, and 76% required clinical safety PMR/PMCs for RA (Table 8a). These results suggested that the FDA evaluated not only the efficacy issues but also safety issues that remained unsolved under AA.

The characteristics of pivotal studies, such as randomization, the number of patients, and endpoints, were identified as factors influencing the decisions about confirmatory and clinical safety PMR/PMCs (Table 9). Moreover, randomization and the number of patients in pivotal studies are closely related to the robustness of the safety evaluation of a clinical study (pivotal study). Hence, it is reasonable that the FDA considers these

factors important when it determines the need for safety evaluation of products in the postmarketing environment.

However, the choice of the endpoint in pivotal studies is not considered directly related to the safety evaluation. The safety evaluation of a drug product should be concluded on the basis of the benefit-risk balance of the product, and the endpoint in pivotal studies is one of the key determining factors for evaluating the efficacy of drug products; this crucial factor might affect the FDA's decision. Moore and Furberg (25) highlighted that several safety questions remained unanswered and that several postmarketing studies were incomplete despite the completion of 5 years since obtaining the approval. Another study evaluating PMR/PMCs suggested that, even after the implementation of FDAAA in 2007, more than 40% of PMR/PMCs had not been started and the number of fulfilled PMR/PMCs remains low (26). Moreover, the study highlighted that 11 of 25 products granted AA were converted to RA after the completion of confirmatory trials during 2006-2017; however, the remaining 14 products still await the confirmation of trials. Hence, we believe that the ongoing monitoring of drug safety after obtaining approval by the FDA should be strengthened under the FDAAA for timely completion of adequate PMR/PMCs.

In conclusion, the characteristics of the pivotal study design that reflects the robustness of the study were identified as critical factors for influencing FDA's decisions to mandate PMR/PMCs, in particular, for significant PMR/PMCs. Given that programs and regulations for PMR/PMCs were intended to confirm safety, efficacy, and labeling issues that were not fully evaluated under preapproval drug development, this is a natural and reasonable situation, which implies that the FDA approved products with surrogate markers and smaller studies but required PMR/PMCs to sufficiently

prove the riskóbenefit profile. Hence, our statistics are consistent with the intended purpose of AA provisions to expedite the approval of drugs for severe and life-threatening diseases.

#### **4. Overall Discussion and Conclusion**

The results of both parts of this research, parts I and II, clarified the FDA's attitude on applying each expedited program for facilitating earlier delivery of drug products, and also the evaluation criteria for issues that remain unsolved until obtaining approval of drug products. That is to say, we revealed that the FDA utilizes the development and review acceleration programs for earlier delivery of desired oncology drug product to cancer patients. Moreover, this research revealed that the FDA had evaluated safety and efficacy issues of oncology drug products, which were delivered earlier, with certain criteria for asking PMR/PMC to companies.

Given the tremendous benefits of expedited programs for oncology product development, companies should take advantage of these programs to deliver desired drug products to patients sooner. At the same time, as these programs have many caveats as well as additional ways to qualify for the benefits, companies should carefully review the guidance to assess the most suitable program for their drug and to ensure all relevant criteria are fulfilled (27).

Moreover, companies should take any possible measures to avoid issues that remain unsolved after approval, especially safety issues. By companies' continuous effort for these measures, in consequence, safety use of desired oncology drug could be achieved.

Nonetheless, possible countermeasures warrant further investigation in the future. For drug products that might require confirmation of safety/efficacy after approval, such as drug products under AA, it is desirable to minimize issues that remain pending after approval by devising drug development program/strategy. One possible countermeasure is making features identified as factors for PMR/PMC, such as randomization, the number of patients, and endpoints, in the pivotal study decision more robust. However,

in either case of AA or OD, the feasibility of these changes is not high from the perspective of the trial duration and cost. For example, a significant number of patient inclusion needs longer patient enrolment period, and randomized study or more robust endpoint requires larger study size and longer study duration. Furthermore, change of endpoints under AA is highly unlikely because of the nature of AA programs that aim to approve drug product with surrogate endpoints.

In contrast, there could be some countermeasure without a change in the clinical trial for safety issues. First, utilization of safety information from parallel development in multiple indications could be a possible option. In recent oncology drug developments, a parallel development in multiple indications is usual for most drug products; hence, it might be a better decision to select a first indication to balance the robustness of the pivotal study design and time of development to minimize safety issues that remain unsolved. In addition, earlier submission of safety information from additional indication program should be beneficial for the evaluation of safety issues and might reduce safety issues that remain unsolved after obtaining approval for the first indication. In fact, some PMR/PMCs analyzed in this research required companies to submit safety data from the clinical study that are not subject to the first indication approval.

Second, continuous efforts to improve the validation of surrogate endpoints are imperative, especially for the AA program, which relies on surrogate endpoints and usually allows smaller trials and shorter completion times. The validation of surrogate endpoints could facilitate the resolution of these issues (4).

Third, the practical use of real-world data, which is one of the trending state-of-the-art technologies, can be a potent tool. Recently, a growing interest has been witnessed in the systematic collection of real-world data to gain further insight into the

impact of newly marketed drugs (28). A recent commentary by Gyawali et al. (29) suggested that real-world evidence can potentially replace highly expensive and resource-intensive randomized clinical trial; however, it cannot yet do so for precision oncology. Moreover, they highlighted that this proper balance between randomized clinical trials and real-world evidence would become increasingly critical in the era of precision medicine.

Finally, we need to seek application of another state-of-the-art technology, a novel safety/efficacy predictor, such as biomarker based on translational research or reverse translational research.

In the future, as the above items become reality, we hope that many oncology drug products will be deliver to patients as early as possible along with necessary and sufficient safety/efficacy information at the time of launch.



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## 7. Appendix

### Appendix 1. List of Approvals for Research Part I

	Approval			Pivotal Study							
Products	Date		Initial	AA/ RA	OD/ non-OD	PR/SR	Randomization	No. of Patient	Endpoint	Review Time (Days)	Development Time (Years)
rituximab	2006-02-10	BLA	No	RA	non-OD	PR	Yes	1854	OS	NA	NA
cetuximab	2006-03-01	BLA	No	RA	OD	PR	Yes	424	OS	NA	NA
decitabine	2006-05-02	NDA	Yes	RA	OD	SR	Yes	170	Response	168	6.50
topotecan hydrochloride	2006-06-14	NDA	No	RA	non-OD	PR	Yes	293	OS	181	NA
bevacizumab	2006-06-20	BLA	No	RA	non-OD	PR	Yes	829	OS	NA	NA
dasatinib	2006-06-28	NDA	Yes	RA	OD	PR	No	445	Response	182	2.90
lenalidomide	2006-06-29	NDA	No	RA	OD	PR	Yes	692	Progression	181	NA
gemcitabine	2006-07-14	NDA	No	RA	non-OD	NA	Yes	356	Progression	392	NA
panitumumab	2006-09-27	BLA	Yes	RA	non-OD	SR	No	463	Progression	183	7.30
imatinib mesylate	2006-09-27	NDA	No	AA	non-OD	PR	No	51	Response	183	NA
rituximab	2006-09-29	BLA	No	RA	non-OD	PR	Yes	322	Progression	NA	NA
vorinostat	2006-10-06	NDA	Yes	RA	OD	PR	No	74	Response	182	6.70
bevacizumab	2006-10-11	BLA	No	RA	non-OD	PR	Yes	878	OS	NA	NA
docetaxel	2006-10-17	NDA	No	RA	non-OD	PR	Yes	358	Progression	183	NA
imatinib mesylate	2006-10-19	NDA	No	RA	OD	SR	No	18	Response	304	NA
imatinib mesylate	2006-10-19	NDA	No	RA	OD	SR	No	31	Response	304	NA
imatinib mesylate	2006-10-19	NDA	No	RA	OD	SR	No	43	Response	302	NA
imatinib mesylate	2006-10-19	NDA	No	RA	OD	NA	No	28	Response	232	NA
imatinib mesylate	2006-10-19	NDA	No	RA	OD	NA	No	176	Response	204	NA
trastuzumab	2006-11-16	BLA	No	RA	non-OD	PR	Yes	3752	Progression	NA	NA
bortezomib	2006-12-08	NDA	No	RA	OD	PR	No	155	Response	182	NA
lapatinib	2007-03-13	NDA	Yes	RA	non-OD	PR	Yes	399	Progression	181	6.20

Appendix 1. List of Approvals for Research Part I (Continued)

Products	Approval			Pivotal Study						Review Time (Days)	Development Time (Years)
	Date		Initial	AA/ RA	OD/ non-OD	PR/SR	Randomization	No. of Patient	Endpoint		
doxorubicin HCl liposome	2007-05-17	NDA	No	RA	OD	PR	Yes	646	Progression	176	NA
temsirolimus	2007-05-30	NDA	Yes	RA	OD	PR	Yes	626	OS	237	9.00
docetaxel	2007-09-28	NDA	No	RA	non-OD	PR	Yes	501	OS	183	NA
cetuximab	2007-10-02	BLA	No	RA	non-OD	PR	Yes	572	OS	NA	NA
ixabepilone	2007-10-16	NDA	Yes	RA	non-OD	PR	Yes	752	Progression	183	8.30
nilotinib	2007-10-29	NDA	Yes	AA	OD	SR	No	337	Response	395	3.50
sorafenib	2007-11-16	NDA	No	RA	OD	PR	Yes	602	Progression	149	NA
bevacizumab	2008-02-22	BLA	No	AA	non-OD	PR	Yes	722	Progression	NA	NA
bendamustine hydrochloride	2008-03-20	NDA	Yes	RA	OD	PR	Yes	301	Response	182	4.80
bortezomib	2008-06-20	NDA	No	RA	OD	PR	Yes	682	Progression	187	NA
pemetrexed	2008-09-26	NDA	No	AA	non-OD	SR	Yes	1725	OS	396	NA
bendamustine hydrochloride	2008-10-31	NDA	No	RA	OD	SR	No	100	Response	308	NA
imatinib mesylate	2008-12-19	NDA	No	AA	OD	PR	Yes	713	Progression	178	NA
degarelix	2008-12-24	NDA	Yes	RA	non-OD	SR	Yes	620	Response	314	7.38
everolimus	2009-03-30	NDA	Yes	RA	non-OD	PR	Yes	416	Progression	276	12.29
bevacizumab	2009-05-05	BLA	No	AA	OD	PR	Yes	223	Response	NA	NA
pemetrexed	2009-07-02	NDA	No	AA	non-OD	NA	Yes	663	OS	261	NA
bevacizumab	2009-07-31	BLA	No	RA	OD	SR	Yes	649	Progression	NA	NA
pralatrexate	2009-09-24	NDA	Yes	AA	OD	PR	No	115	Response	185	12.57
pazopanib	2009-10-19	NDA	Yes	RA	non-OD	NA	Yes	435	Progression	305	7.03
ofatumumab	2009-10-26	BLA	Yes	AA	OD	PR	No	154	Response	269	5.35
romidepsin	2009-11-05	NDA	Yes	RA	OD	SR	No	167	Response	297	7.44

Appendix 1. List of Approvals for Research Part I (Continued)

Approval			Pivotal Study							Review Time (Days)	Development Time (Years)
Products	Date	Initial	AA/ RA	OD/ non-OD	PR/SR	Randomization	No. of Patient	Endpoint			
lapatinib	2010-01-29	NDA	No	AA	non-OD	SR	Yes	1278	Progression	304	NA
rituximab	2010-02-18	BLA	No	RA	OD	PR	Yes	960	Progression	276	NA
erlotinib	2010-04-16	NDA	No	RA	non-OD	SR	Yes	889	Progression	394	NA
cabazitaxel	2010-06-17	NDA	Yes	RA	non-OD	PR	Yes	755	OS	78	11.64
nilotinib	2010-06-17	NDA	No	AA	non-OD	PR	Yes	846	Response	178	NA
dasatinib	2010-10-28	NDA	No	AA	non-OD	PR	Yes	519	Response	183	NA
trastuzumab	2010-10-29	BLA	No	RA	OD	SR	Yes	594	OS	192	NA
everolimus	2010-10-29	NDA	No	AA	OD	PR	No	28	Response	182	NA
eribulin mesylate	2010-11-15	NDA	Yes	RA	non-OD	PR	Yes	762	OS	230	7.55
rituximab	2011-01-28	BLA	No	RA	non-OD	SR	Yes	1018	Progression	303	NA
ipilimumab	2011-03-25	BLA	Yes	RA	OD	PR	Yes	676	OS	273	10.63
vandetanib	2011-04-06	NDA	Yes	RA	OD	PR	Yes	331	Progression	273	10.98
abiraterone acetate	2011-04-28	NDA	Yes	RA	non-OD	PR	Yes	1195	OS	131	5.27
everolimus	2011-05-05	NDA	No	RA	OD	NA	Yes	410	Progression	181	NA
sunitinib malate	2011-05-20	NDA	No	RA	non-OD	PR	Yes	171	Progression	168	NA
romidepsin	2011-06-16	NDA	No	AA	OD	PR	No	131	Response	181	NA
vemurafenib	2011-08-17	NDA	Yes	RA	OD	PR	Yes	675	OS	112	4.88
brentuximab vedotin	2011-08-19	BLA	Yes	AA	OD	PR	No	102	Response	175	5.15
crizotinib	2011-08-26	NDA	Yes	AA	OD	PR	No	255	Response	149	5.62
cetuximab	2011-11-07	BLA	No	RA	non-OD	PR	Yes	442	OS	1165	NA
ruxolitinib	2011-11-16	NDA	Yes	RA	OD	PR	Yes	528	Response	166	4.55
axitinib	2012-01-27	NDA	Yes	RA	non-OD	SR	Yes	723	Progression	288	10.16
vismodegib	2012-01-30	NDA	Yes	RA	non-OD	PR	No	104	Response	144	5.24
everolimus	2012-04-26	NDA	No	AA	OD	PR	Yes	118	Response	129	NA



Appendix 1. List of Approvals for Research Part I (Continued)

Products	Approval			Pivotal Study						Review	Development
	Date		Initial	AA/ RA	OD/ non-OD	PR/SR	Randomization	No. of Patient	Endpoint	Time (Days)	Time (Years)
pazopanib	2012-04-26	NDA	No	RA	OD	SR	Yes	369	Progression	303	NA
pertuzumab	2012-06-08	BLA	Yes	RA	non-OD	PR	Yes	808	Progression	185	10.95
cetuximab	2012-07-06	BLA	No	RA	non-OD	SR	Yes	1217	OS	303	NA
carfilzomib	2012-07-20	NDA	Yes	AA	OD	SR	No	266	Response	298	7.02
everolimus	2012-07-20	NDA	No	RA	non-OD	SR	Yes	724	Progression	260	NA
ziv-aflibercept	2012-08-03	BLA	Yes	RA	non-OD	PR	Yes	1226	OS	183	10.93
vincristine sulfate liposome	2012-08-09	NDA	Yes	AA	OD	SR	No	65	Response	394	12.79
everolimus	2012-08-29	NDA	No	AA	non-OD	SR	Yes	117	Response	182	NA
enzalutamide	2012-08-31	NDA	Yes	RA	non-OD	PR	Yes	1199	OS	102	9.35
bosutinib	2012-09-04	NDA	Yes	RA	OD	SR	No	546	Response	292	8.33
regorafenib	2012-09-27	NDA	Yes	RA	non-OD	PR	Yes	760	OS	153	6.11
paclitaxel protein-bound particles	2012-10-11	NDA	No	RA	non-OD	SR	Yes	1052	Response	304	NA
omacetaxine mepesuccinate	2012-10-26	NDA	Yes	AA	OD	SR	No	111	Response	210	11.46
cabozantinib	2012-11-29	NDA	Yes	RA	non-OD	PR	Yes	330	Progression	192	7.42
abiraterone acetate	2012-12-10	NDA	No	RA	non-OD	PR	Yes	1088	Progression	179	NA
ponatinib	2012-12-14	NDA	Yes	AA	OD	PR	No	449	Response	137	4.99
bevacizumab	2013-01-23	BLA	No	RA	non-OD	PR	Yes	820	OS	170	NA
pomalidomide	2013-02-08	NDA	Yes	AA	OD	SR	Yes	221	Response	304	10.17
ado-trastuzumab	2013-02-22	BLA	Yes	RA	non-OD	PR	Yes	991	OS	182	7.15
erlotinib	2013-05-14	NDA	No	RA	non-OD	PR	Yes	174	Progression	179	NA
radium Ra 223 dichloride	2013-05-15	NDA	Yes	RA	non-OD	PR	Yes	541	OS	152	5.32

Appendix1. List of Approvals for Research Part I (Continued)

	Approval			Pivotal Study								
Products	Date		Initial	AA/ RA	OD/ non-OD	PR/SR	Randomization	No. of Patient	Endpoint	Review Time (Days)	Development Time (Years)	
dabrafenib	2013-05-29	NDA	Yes	RA	OD	SR	Yes	250	Progression	304	3.85	
trametinib	2013-05-29	NDA	Yes	RA	OD	SR	Yes	322	Progression	300	5.04	
lenalidomide	2013-06-05	NDA	No	RA	OD	PR	No	134	Response	182	NA	
afatinib	2013-07-12	NDA	Yes	RA	OD	PR	Yes	345	Progression	240	9.54	
paclitaxel protein-bound particles	2013-09-06	NDA	No	RA	OD	PR	Yes	861	OS	169	NA	
pertuzumab	2013-09-30	BLA	No	AA	non-OD	PR	Yes	417	Response	152	NA	
obinutuzumab	2013-11-01	BLA	Yes	RA	OD	PR	Yes	356	Progression	193	4.66	
ibrutinib	2013-11-13	NDA	Yes	AA	OD	PR	No	111	Response	138	5.18	
sorafenib	2013-11-22	NDA	No	RA	OD	PR	Yes	417	Progression	150	NA	
trametinib	2014-01-08	NDA	No	AA	OD	PR	No	162	Response	184	NA	
dabrafenib	2014-01-09	NDA	No	AA	non-OD	PR	Yes	162	Response	185	NA	
ibrutinib	2014-02-12	NDA	No	AA	OD	PR	No	48	Response	229	NA	
ofatumumab	2014-04-17	BLA	No	RA	OD	PR	Yes	447	Progression	181	NA	
ramucirumab	2014-04-21	BLA	Yes	RA	OD	PR	Yes	355	OS	241	9.65	
siltuximab	2014-04-23	BLA	Yes	RA	OD	PR	Yes	79	Response	237	5.68	
ceritinib	2014-04-29	NDA	Yes	AA	OD	PR	No	163	Response	126	3.47	
belinostat	2014-07-03	NDA	Yes	AA	OD	PR	No	120	Response	207	9.55	
idelalisib	2014-07-23	NDA	Yes	AA	OD	SR	Yes	220	Progression	315	6.07	
bevacizumab	2014-08-14	BLA	No	RA	non-OD	PR	Yes	452	OS	112	NA	
pembrolizumab	2014-09-04	BLA	Yes	AA	OD	PR	No	173	Response	189	3.65	
ramucirumab	2014-11-05	BLA	No	RA	OD	SR	Yes	665	OS	183	NA	
bevacizumab	2014-11-14	BLA	No	RA	non-OD	PR	Yes	361	Progression	178	NA	
blinatumomab	2014-12-03	BLA	Yes	AA	OD	PR	No	185	Response	75	7.80	

ramucirumab	2014-12-12	BLA	No	RA	non-OD	PR	Yes	1253	OS	169	NA
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Appendix 1. List of Approvals for Research Part I (Continued)

Products	Approval			Pivotal Study						Review Time (Days)	Development Time (Years)
	Date		Initial	AA/ RA	OD/ non-OD	PR/SR	Randomization	No. of Patient	Endpoint		
lanreotide	2014-12-16	NDA	No	RA	OD	PR	Yes	204	Progression	169	NA
olaparib	2014-12-19	NDA	Yes	AA	OD	PR	No	137	Response	319	8.30
nivolumab	2014-12-22	BLA	Yes	AA	OD	PR	Yes	370	Response	145	8.32
ibrutinib	2015-01-29	NDA	No	RA	OD	PR	No	63	Response	104	NA
palbociclib	2015-02-03	NDA	Yes	AA	non-OD	PR	Yes	165	Progression	174	10.83
lenvatinib	2015-02-13	NDA	Yes	RA	OD	PR	Yes	392	Progression	183	9.79
panobinostat	2015-02-23	NDA	Yes	AA	OD	PR	Yes	193	Progression	338	11.87
dinutuximab	2015-03-10	BLA	Yes	RA	OD	PR	Yes	226	OS	333	23.19
ramucirumab	2015-04-24	BLA	No	RA	non-OD	SR	Yes	1072	OS	65	NA
gefitinib	2015-07-13	NDA	No	RA	OD	SR	No	106	Response	299	NA
carfilzomib	2015-07-24	NDA	No	RA	non-OD	PR	Yes	792	Progression	179	NA
sonidegib	2015-07-24	NDA	Yes	RA	non-OD	SR	Yes	230	Response	301	6.60
brentuximab vedotin	2015-08-17	BLA	No	RA	OD	PR	Yes	329	Progression	180	NA
trifluridine-tipiracil	2015-09-22	NDA	Yes	RA	non-OD	SR	Yes	800	OS	277	16.66
nivolumab	2015-09-30	BLA	No	AA	OD	PR	Yes	142	Progression	184	NA
pembrolizumab	2015-10-02	BLA	No	AA	non-OD	PR	No	61	Response	183	NA
nivolumab	2015-10-09	BLA	No	RA	non-OD	PR	Yes	582	OS	99	NA
irinotecan liposome injection	2015-10-22	NDA	No	RA	OD	PR	Yes	417	OS	181	NA
trabectedin	2015-10-23	NDA	Yes	RA	OD	PR	Yes	518	Progression	333	19.47
ipilimumab	2015-10-28	BLA	No	RA	OD	SR	Yes	951	other	303	NA
cobimetinib	2015-11-10	NDA	Yes	RA	OD	PR	Yes	495	OS	334	8.81
osimertinib	2015-11-13	NDA	Yes	AA	non-OD	PR	No	411	Response	161	2.34

daratumumab	2015-11-16	BLA	Yes	AA	OD	PR	No	106	Response	130	8.00
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Appendix 1. List of Approvals for Research Part I (Continued)

Products	Approval			Pivotal Study				No. of Patient	Endpoint	Review Time (Days)	Development Time (Years)
	Date		Initial	AA/ RA	OD/ non-OD	PR/SR	Randomization				
trametinib	2015-11-20	NDA	No	RA	non-OD	PR	Yes	423	OS	182	NA
ixazomib	2015-11-20	NDA	Yes	RA	OD	PR	Yes	722	Progression	133	6.56
nivolumab	2015-11-23	BLA	No	RA	non-OD	PR	Yes	821	OS	68	NA
necitumumab	2015-11-24	BLA	Yes	RA	OD	SR	Yes	1093	OS	357	6.94
elotuzumab	2015-11-30	BLA	Yes	RA	non-OD	PR	Yes	646	Progression	156	9.34
alectinib	2015-12-11	NDA	Yes	AA	OD	PR	No	225	Response	158	4.12
ofatumumab	2016-01-19	BLA	No	RA	OD	PR	Yes	474	Progression	181	NA
eribulin	2016-01-28	NDA	No	RA	OD	PR	Yes	446	OS	183	NA
palbociclib	2016-02-19	NDA	No	RA	non-OD	PR	Yes	521	Progression	127	NA
obinutuzumab	2016-02-26	BLA	No	RA	non-OD	PR	No	321	Progression	182	NA
everolimus	2016-02-26	NDA	No	RA	OD	PR	No	302	Progression	183	NA
crizotinib	2016-03-11	NDA	No	RA	non-OD	PR	No	50	Response	155	NA
venetoclax	2016-04-11	NDA	Yes	RA	OD	PR	No	240	Response	165	5.37
cabozantinib	2016-04-25	NDA	No	RA	non-OD	PR	Yes	375	Progression	125	NA
lenvatinib	2016-05-13	NDA	No	RA	non-OD	PR	Yes	153	Progression	179	NA
nivolumab	2016-05-17	BLA	No	AA	OD	PR	No	263	Response	77	NA
atezolizumab	2016-05-18	BLA	Yes	AA	non-OD	PR	No	310	Response	127	5.02
pembrolizumab	2016-08-05	BLA	No	RA	non-OD	PR	No	174	Response	178	NA
erlotinib	2016-10-18	NDA	No	RA	non-OD	SR	Yes	643	OS	305	NA
atezolizumab	2016-10-18	NDA	No	RA	non-OD	PR	Yes	1137	OS	242	NA
olaratumab	2016-10-19	BLA	Yes	AA	OD	PR	Yes	133	OS	238	2.59
pembrolizumab	2016-10-24	BLA	No	RA	non-OD	PR	Yes	305	OS	122	NA
nivolumab	2016-11-10	BLA	No	RA	non-OD	PR	Yes	361	OS	183	NA
daratumumab	2016-11-21	BLA	No	RA	OD	PR	Yes	498	Progression	96	NA

daratumumab	2016-11-21	BLA	No	RA	OD	PR	Yes	569	Progression	96	NA
rucaparib	2016-12-19	NDA	Yes	AA	OD	PR	No	106	Response	179	7.32

## Appendix2. List of Approvals for Research Part II

Products	Approval	Pivotal Study				PMR/PMC*						Score
	Date	AA/ RA	OD/ non-OD	PR/ SR	Randomization	No. of Patient	Endpoint	C	CS	CP	OT	
degarelix	2008-12-24	RA	non-OD	SR	Yes	620	Response	No	Yes	No	No	5
everolimus	2009-03-30	RA	non-OD	PR	Yes	416	Progression	Yes	Yes	Yes	Yes	15
pralatrexate	2009-09-24	AA	OD	PR	No	115	Response	Yes	Yes	Yes	Yes	30
pazopanib	2009-10-19	RA	non-OD	NA	Yes	435	Progression	Yes	Yes	Yes	Yes	40
ofatumumab	2009-10-26	AA	OD	PR	No	154	Response	Yes	Yes	No	Yes	33
romidepsin	2009-11-05	RA	OD	SR	No	167	Response	No	Yes	Yes	Yes	44
cabazitaxel	2010-06-17	RA	non-OD	PR	Yes	755	OS	Yes	Yes	Yes	Yes	57
eribulin mesylate	2010-11-15	RA	non-OD	PR	Yes	762	OS	Yes	Yes	Yes	No	16
ipilimumab	2011-03-25	RA	OD	PR	Yes	676	OS	Yes	Yes	No	Yes	34
vandetanib	2011-04-06	RA	OD	PR	Yes	331	Progression	Yes	Yes	No	Yes	22
abiraterone acetate	2011-04-28	RA	non-OD	PR	Yes	1195	OS	No	No	Yes	Yes	22
vemurafenib	2011-08-17	RA	OD	PR	Yes	675	OS	Yes	Yes	Yes	Yes	51
brentuximab vedotin	2011-08-19	AA	OD	PR	No	102	Response	Yes	Yes	No	No	19
crizotinib	2011-08-26	AA	OD	PR	No	255	Response	Yes	Yes	Yes	Yes	70
ruxolitinib	2011-11-16	RA	OD	PR	Yes	528	Response	Yes	Yes	No	No	30
axitinib	2012-01-27	RA	non-OD	SR	Yes	723	Progression	No	No	No	No	0
vismodegib	2012-01-30	RA	non-OD	PR	No	104	Response	No	Yes	Yes	Yes	39
pertuzumab	2012-06-08	RA	non-OD	PR	Yes	808	Progression	Yes	Yes	No	Yes	16
carfilzomib	2012-07-20	AA	OD	SR	No	266	Response	Yes	Yes	Yes	No	41
ziv-aflibercept	2012-08-03	RA	non-OD	PR	Yes	1226	OS	No	No	No	Yes	3
vincristine sulfate liposome	2012-08-09	AA	OD	SR	No	65	Response	Yes	Yes	No	Yes	14
enzalutamide	2012-08-31	RA	non-OD	PR	Yes	1199	OS	No	Yes	Yes	Yes	34
bosutinib	2012-09-04	RA	OD	SR	No	546	Response	Yes	Yes	Yes	No	11

\* C: Confirmatory, CS: Clinical Safety, CP: Clinical Pharmacology, OT: Others

Appendix2. List of Approvals for Research Part II (Continued)

Products	Approval	Pivotal Study				PMR/PMC						Score
	Date	AA/ RA	OD/ non-OD	PR/ SR	Randomization	No. of Patient	Endpoint	C	CS	CP	OT	
regorafenib	2012-09-27	RA	non-OD	PR	Yes	760	OS	No	Yes	Yes	No	24
omacetaxine mepesuccinate	2012-10-26	AA	OD	SR	No	111	Response	Yes	Yes	Yes	No	18
cabozantinib	2012-11-29	RA	non-OD	PR	Yes	330	Progression	Yes	Yes	Yes	Yes	42
ponatinib	2012-12-14	AA	OD	PR	No	449	Response	Yes	Yes	Yes	Yes	50
pomalidomide	2013-02-08	AA	OD	SR	Yes	221	Response	Yes	Yes	Yes	No	60
ado-trastuzumab	2013-02-22	RA	non-OD	PR	Yes	991	OS	No	No	Yes	Yes	25
radium Ra 223 dichloride	2013-05-15	RA	non-OD	PR	Yes	541	OS	No	Yes	No	No	23
dabrafenib	2013-05-29	RA	OD	SR	Yes	250	Progression	No	Yes	Yes	No	56
trametinib	2013-05-29	RA	OD	SR	Yes	322	Progression	No	Yes	Yes	No	21
afatinib	2013-07-12	RA	OD	PR	Yes	345	Progression	Yes	Yes	Yes	No	11
obinutuzumab	2013-11-01	RA	OD	PR	Yes	356	Progression	No	No	No	No	0
ibrutinib	2013-11-13	AA	OD	PR	No	111	Response	Yes	Yes	Yes	Yes	51
ramucirumab	2014-04-21	RA	OD	PR	Yes	355	OS	No	No	No	Yes	8
siltuximab	2014-04-23	RA	OD	PR	Yes	79	Response	No	Yes	No	No	5
ceritinib	2014-04-29	AA	OD	PR	No	163	Response	Yes	Yes	Yes	No	36
belinostat	2014-07-03	AA	OD	PR	No	120	Response	Yes	Yes	Yes	Yes	47
idelalisib	2014-07-23	AA	OD	SR	Yes	220	Progression	Yes	Yes	No	No	48
pembrolizumab	2014-09-04	AA	OD	PR	No	173	Response	Yes	Yes	No	Yes	9
blinatumomab	2014-12-03	AA	OD	PR	No	185	Response	Yes	Yes	No	No	6
olaparib	2014-12-19	AA	OD	PR	No	137	Response	Yes	Yes	No	No	27
nivolumab	2014-12-22	AA	OD	PR	Yes	370	Response	Yes	Yes	No	No	6
palbociclib	2015-02-03	AA	non-OD	PR	Yes	165	Progression	Yes	Yes	No	No	20
lenvatinib	2015-02-13	RA	OD	PR	Yes	392	Progression	No	Yes	No	No	6
panobinostat	2015-02-23	AA	OD	PR	Yes	193	Progression	Yes	Yes	No	No	13

\* C: Confirmatory, CS: Clinical Safety, CP: Clinical Pharmacology, OT: Others

Appendix2. List of Approvals for Research Part II (Continued)

Products	Approval		Pivotal Study				PMR/PMC					
	Date	AA/ RA	OD/ non-OD	PR/ SR	Randomization	No. of Patient	Endpoint	C	CS	CP	OT	Score
sinutuximab	2015-03-10	RA	OD	PR	Yes	226	OS	No	Yes	No	Yes	24
aonidegib	2015-07-24	RA	non-OD	SR	Yes	230	Response	No	Yes	Yes	Yes	25
trifluridine-tipiracil	2015-09-22	RA	non-OD	SR	Yes	800	OS	No	No	Yes	No	10
rrabectedin	2015-10-23	RA	OD	PR	Yes	518	Progression	No	Yes	Yes	No	10
xobimetinib	2015-11-10	RA	OD	PR	Yes	495	OS	Yes	Yes	Yes	No	15
osimertinib	2015-11-13	AA	non-OD	PR	No	411	Response	Yes	Yes	Yes	No	28
saratumumab	2015-11-16	AA	OD	PR	No	106	Response	Yes	Yes	No	Yes	29
ixazomib	2015-11-20	RA	OD	PR	Yes	722	Progression	No	No	No	No	0
necitumumab	2015-11-24	RA	OD	SR	Yes	1093	OS	No	No	No	No	0
wlotuzumab	2015-11-30	RA	non-OD	PR	Yes	646	Progression	Yes	Yes	No	No	5
lectinib	2015-12-11	AA	OD	PR	No	225	Response	Yes	Yes	Yes	No	11
venetoclax	2016-04-11	RA	OD	PR	No	240	Response	Yes	Yes	Yes	No	18
tezolizumab	2016-05-18	AA	non-OD	PR	No	310	Response	Yes	Yes	No	Yes	26
olaratumab	2016-10-19	AA	OD	PR	Yes	133	OS	Yes	Yes	No	No	7
eucaparib	2016-12-19	AA	OD	PR	No	106	Response	Yes	Yes	Yes	Yes	30

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