Research on single-arm trials for obtaining regulatory approval of new anticancer drugs

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Abstract

In recent years, an increasing number of anticancer drugs have been approved based on the results of a single-arm trial (SAT). The magnitude of the objective response rate (ORR) in SATs is important for regulatory decisions, but there has been no clear guidance specifying the degree of ORR for approval. In the United States (US), accelerated approval (AA) program expedites access to promising drugs for life-threatening conditions, particularly in oncology. In this program, a new drug is evaluated based on a surrogate endpoint, ORR in oncology. However, challenges arise from the trade-off between faster access and the certainty of clinical benefits.

The purpose of this research was to identify issues to be considered mainly from the perspective of efficacy evaluation when proceeding with a development plan to obtain approval based on a SAT as the pivotal study data. In Research 1, new anticancer drugs approved in the US based on SAT data were studied to determine the magnitude of ORR required for approval under the SAT by selecting one control treatment among available therapies and comparing the ORR between the control and the new drug. In Research 2, with regard to indications that received AA based on the SAT, characteristics of indications that were successfully converted to regular approval (RA) and withdrawn based on the subsequent confirmatory trials were compared.

In Research 1, all anticancer drugs approved by the US Food and Drug Administration (FDA) between January 2016 and December 2019 were identified through the FDA website. From these, we selected drugs approved for solid tumors based on SATs. For each indication, one regimen was selected from the standard-of-care as a best comparison therapy (BCT), which was defined as the latest standard regimen for the same tumor and treatment line. Of the 31 solid tumor indications identified, we selected

BCT for 28 indications. In 23 of the 28 indications (82.1%), ORR of the investigated product exceeded that of the BCT, and in 16 of these (69.6%), the lower limit of the 95% confidence interval (CI) of the ORR of the investigated product exceeded the point estimate of the ORR of the BCT. For seven products, the lower limit of the 95% CI was below the point estimate of the ORR of the BCT, with differences ranging from 1.0% to 3.4%. Thus, the lower limit of a 95% CI of the ORR of a new drug in an SAT exceeding the point estimate of the BCT ORR could be an important factor in obtaining regulatory approval.

In Research 2, we used the same dataset for Research 1. From the dataset, we selected drugs granted AA for solid tumors based on a single-arm trial. We compared the characteristics of the AA and confirmatory trials between products that were successfully converted to RA and those that were withdrawn. Twenty-four AA indications were identified, of which 11 were converted to RA and 6 were withdrawn. The magnitude of the ORR in both the AA and confirmatory trials was not a factor that clearly determined the conversion or withdrawal of AA. However, if the experimental arm did not achieve a certain level of ORR over the control arm in the confirmatory trial, it was thought to increase the uncertainty of successful conversion to RA. Therefore, a relatively high ORR compared with that of the control arm in the confirmatory trial, after AA, is important for successfully obtaining RA.

Through the present research, it was confirmed that clinically meaningful ORR is an important endpoint not only for SATs but also for subsequent confirmatory trials in a development plan aiming for approval based on SAT data as a pivotal trial.

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Abbreviations

AA	Accelerated approval
AA trial	Pivotal trial for accelerated approval
ALK	Anaplastic lymphoma kinase
BCT	Best comparison therapy
BRAF	v-RAF murine sarcoma viral oncogene homolog B1
BRCA	Breast cancer susceptibility gene
CI	Confidence interval
CPSs	Combined positive scores
CSCC	Cutaneous squamous cell carcinoma
CT	Computed tomography
DFS	Disease free survival
dMMR	DNA mismatch-repair deficient
DOR	Duration of response
EGFR	epidermal growth factor receptor
ESMO-MCBS	European Society for Medical Oncology Magnitude of Clinical Benefit Scale
FDA	Food and Drug Administration
FGFR	Fibroblast growth factor receptor
HCC	Hepatocellular carcinoma
HER2	Human epidermal growth factor receptor
HRD	Homologous recombination deficiency
HR	Hormone receptor

ICI	Immune checkpoint inhibitor
MCC	Merkel cell carcinoma
MOA	Mechanism of action
MSI-H	Microsatellite instability-high
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NDA	New drug application
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PFS	Progression free survival
RA	Regular approval
RCT	Randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	c-ros oncogene 1
SAT	Single-arm trial
SCLC	Small cell lung cancer
UC	Urothelial carcinoma
US	United States

1. Introduction

Clinical development of an anticancer drug is a stepwise process from exploratory trials to confirmatory trials that evaluate efficacy and safety [1]. However, anticancer drugs have increasingly been approved based on a single-arm trial (SAT), an exploratory trial, in these days [2]. Advances in medicine and technology leading to development of effective drugs and genomic diagnostics for rare cancers and fractions underlie this trend. Thus, the number of SAT-based approvals is expected to increase.

The primary endpoint used in SATs is the objective response rate (ORR). To demonstrate a clinical significance of ORR, expected response rate of a new drug must exceed a threshold, which is set based on the response rate of a standard-of-care. The magnitude of ORR is important, and in general, decisions are made based on a high ORR [3]. However, because the magnitude of a clinically meaningful ORR expected for a new drug differs depending on the cancer type and line of treatment, the magnitude of an ORR required for approval differs depending on each indication. There are currently no clear guidelines specifying the degree of the ORR for regulatory approval, and reviews are conducted based on the situation of individual drugs.

The accelerated approval (AA) regulation [4], which was created in 1992 by the Food and Drug Administration (FDA) in the United States (US), is a program that allows faster availability of promising new drugs for patients with life-threatening conditions or unmet medical needs. In this program, a new drug is evaluated based on a surrogate endpoint that is reasonably likely to predict clinical benefit and that can be measured earlier compared to the case where a real clinical benefit is assessed in a long term and large-scale trial [5]. Therefore, one or some trials to confirm the real clinical benefit are legally required after AA, and if the confirmatory trial demonstrated the drug's clinical

benefit, regular approval (RA) will be granted; if it fails to demonstrate it, the AA will be withdrawn [5]. In recent years, drug development based on the AA program has been increasing, mostly for anticancer drugs, and accordingly, the withdrawal is also increasing. Although SAT and randomized controlled trial (RCT) have different primary endpoints, it is unclear whether the clinical benefit estimated by SAT was adequately demonstrated in the confirmatory trial.

This research focused on new drug development in the US. The US is a country where the largest number of new drugs have been developed ahead of the rest of the world, and there have been many new drug applications and approvals based on single-arm trial data through a special review pathway such as AA. In addition, the US has the largest pharmaceutical market in the world. Thus, understanding new drug development in the US is important for all pharmaceutical companies developing new drugs globally.

The purpose of this research was to identify issues to be considered mainly from the perspective of efficacy evaluation when proceeding with a development plan to obtain approval based on SAT as the pivotal study data. In Research 1, new anticancer drugs approved in the US based on SAT data were studied to determine the magnitude of ORR required for approval under the SAT by selecting one control treatment among available therapies and comparing the ORR of the control treatment with that of the new drug. Then, in Research 2, with regard to indications that received AA based on the SAT, characteristics of indications that were successfully converted to RA and those withdrawn based on the subsequent confirmatory trials were compared.

2. Response rate of anticancer drugs approved by the Food and Drug Administration based on a single-arm trial (Research 1)

2.1. Background

Development of an anticancer drug from inception through efficacy and safety evaluation is a stepwise process [1]. The maximum tolerated dose is explored in phase I studies, and the efficacy and safety of the dosage and administration thus determined are investigated in a targeted patient population in phase II studies. Subsequently, phase III studies are conducted to compare the efficacy and safety of the new drug against a standard treatment.

Since the 1980s, new anticancer drugs have been approved based on direct clinical benefits, such as prolonged survival and improved quality of life [6]. Typically, obtaining regulatory approval for new anticancer drugs involved demonstrating favorable results in RCTs with a primary endpoint, such as overall survival (OS). Approval was sometimes granted based on the results of a phase II study with a SAT design (without control arms), due to the difficulty in conducting RCTs for cancers with a small number of patients or for rare fractions with infrequent genetic abnormalities. Recently, anticancer drugs have increasingly been approved based on an SAT [2].

Different filing strategies can be adopted for each drug; some require confirmatory phase III studies for filing, and some are accepted for filing with an earlier exploratory phase II study. In either case, a pivotal trial must show clinical benefits in the targeted patient population. The true endpoint for anticancer drugs is OS. To confirm this clinical benefit, RCTs should be conducted with a sample size that is calculated by setting statistically appropriate power and significance levels, so that superiority or non-inferiority of the new drug over the control arm can be tested. Moreover, subjects should

be randomized by considering important prognostic factors.

In contrast, the primary endpoint used in SATs is the ORR. The Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.1 [7] is commonly used for evaluation of ORRs. Evaluation involves measuring the tumor diameter based on computed tomography (CT) and/or other images, with evaluator-dependent results. Thus, evaluation by investigators may be biased, and hence ORRs evaluated by blinded independent central review are often used as a primary endpoint. Regulatory review, based on data from SATs, has to be conducted with limited information, because the ORR does not necessarily correlate with OS, depending on the cancer type. However, the ORR has advantages for the development of new drugs for rare cancers, where evaluation of the OS benefit compared to a standard-of-care is difficult. This approach can reduce development costs, shorten development time, and accelerate patient access to new drugs.

The guidance document on expedited programs for serious conditions by the US FDA [5] states that "radiographic evidence of tumor shrinkage (response rate) in certain cancer types has been considered reasonably likely to predict an improvement in overall survival" as an example of an endpoint for approval by the AA scheme. Another guideline [6] states that "the FDA has sometimes accepted ORR and the response duration observed in single-arm studies as substantial evidence supporting accelerated approval." Consequently, the magnitude of the ORR is important, and in general, decisions are made based on a high ORR [3]. However, because the magnitude of a clinically meaningful ORR expected for a new drug differs depending on the cancer type and line of treatment, the magnitude of an ORR required for approval differs depending on each indication. There are currently no clear guidelines specifying the degree of the ORR for regulatory approval, and reviews are conducted for individual drug situations. Additionally, no study

has investigated the difference in the ORRs of an approved drug and a historical control.

Research 1 explored the magnitude of the ORR necessary for granting regulatory approval by comparing the ORR of an anticancer drug approved by the FDA, based on SATs, with that of the standard-of-care that was considered as a historical control for the drug.

2.2. Methods

Identification of products to be investigated and acquisition of relevant information

All anticancer drugs, including those for additional indications, approved by the FDA between January 2016 and December 2019, were identified through the FDA's Hematology/Oncology (Cancer) Approvals & Safety Notifications website [8], as of January 2020. If multiple indications were approved for a single product on the same day, each indication was counted separately. We excluded approvals for cellular and gene therapies, approvals with no anticancer effect indications, and those related to hematological malignancies, to extract approvals for indications for solid tumors. Next, we selected SAT-based (without control arms) approvals, by referring to the design of the pivotal trial on which approval was based. Among these, approvals for tumor agnostic indications and indications for which the ORR was not the primary endpoint were excluded, as we could not compare the ORR of the product with that of the standard-of-care.

We obtained data on the ORR and 95% confidence interval (CI) in the pivotal SAT from the product label. We also collected information on the indication and the mechanism of action (MOA) of the product from the label and on the application of special programs, such as breakthrough therapy designation, AA, fast track, priority

review, and orphan drug designation, from the approval announcement for the product on the FDA website [8].

Selection of the BCT and acquisition of relevant information

For each of the investigated products and approved indications, best comparison therapy (BCT) information was referenced to the most recent National Comprehensive Cancer Network clinical practice guidelines in oncology (NCCN guidelines) at the time of its approval. For original new drug applications for which the review report was available on the FDA website [9], we also referred to the treatment options listed in Chapter 2.2, "Analysis of current treatment options," of the review report. For products and approved indications for which publications of the pivotal trial results were available, treatments listed as comparators in the introduction or discussion sections of the published articles were also referenced.

For each of the investigated products, we first identified the standard-of-care for the target tumor and treatment line. In cases where the patient population was limited by biomarkers and where there was no similar drug for populations with the same biomarkers, the drug was considered as first-in-class, and the standard-of-care used for patients not stratified by the biomarkers was considered to be a BCT. Second, in cases where there were multiple competing standard-of-care regimens, the most current regimen at the time of approval was selected as a BCT.

Analysis

A scatter plot was created by comparing the ORR of the investigated product (with its 95% CI) with that of the BCT. No statistical analyses or tests were performed.

2.3. Results

Identification of investigated products

We identified 155 anticancer drug approvals between January 2016 and December 2019. We excluded three approvals for cellular therapy (two of tisagenlecleucel and one of axicabtagene ciloleucel), and four approvals related to indirect anticancer effects (subcutaneous use of a rituximab plus hyaluronidase combination for follicular lymphoma, diffuse large B-cell lymphoma, and chronic lymphocytic leukemia, subcutaneous use of trastuzumab plus hyaluronidase-oysk for breast cancer, lower-dose cabazitaxel for prostate cancer, and longer-acting calaspargase pegol-mknl for acute lymphoblastic leukemia). Forty-seven approvals for hematological malignancy were also excluded.

Among 101 indications for solid tumors, approval was SAT-based for 35 and RCT-based for 66. From the 35 SAT approvals, three approvals of pembrolizumab, larotrectinib, and entrectinib for tumor agnostic indications were excluded, due to difficulty in comparing the results for each indication. One approval of iobenguane I131 was excluded because an endpoint other than the ORR was evaluated for approval. Consequently, 31 indications for solid tumors that were approved based on the SAT results were identified in this research (Fig. 1).

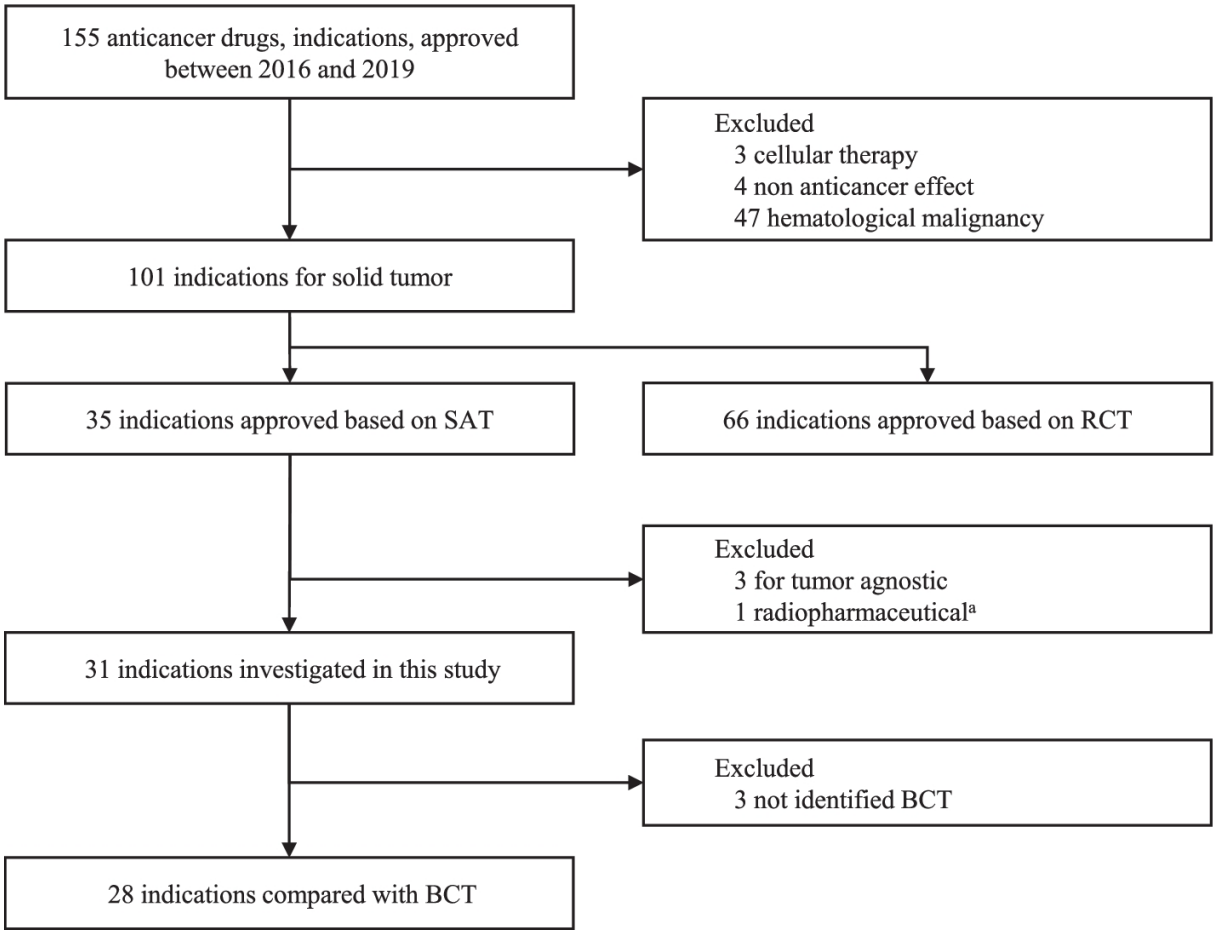


Figure 1 Identification of investigated products for Research 1

Abbreviations：ORR overall response rate, RCT randomized controlled trial, SAT single-arm trial, BCT best comparison therapy

[a] ORR was not the primary endpoint in the pivotal SAT

Characteristics of approved indications for solid tumors

Table 1 shows the characteristics of approved indications for solid tumors: 35 were SAT- based and 66 were RCT-based. With regard to the cancer type for which the indication was approved, the cancer types with the highest number of indications approved based on RCTs were lung cancer (15 approvals [22.7%]) and breast cancer (14 [21.2%]), while the cancer types with the highest number of indications with SAT-based

approval were lung cancer (8 [22.9%]) and bladder cancer (7 [20.0%]). For kidney cancer, prostate cancer, and neuroendocrine tumors, no drug was approved based on SAT results. On the other hand, all drugs for tissue/site agnostic indications and for colorectal cancer were approved based on SAT results.

With regard to the MOA of the drug, molecular targeted agents accounted for 51.5% (34/66) among the RCT-based approvals, while immune checkpoint inhibitors accounted for 51.4% (18/35) among the SAT-based approvals. No androgen receptor inhibitors were approved based on SAT results.

Among the 35 approved indications based on SATs, 22 (62.9%) had breakthrough therapy designation, 26 (74.3%) obtained AA, and 34 (97.1%) were subject to priority review.

Table 1 Characteristics of oncology drug approvals

		SAT n (%) n = 35	RCT n (%) n = 66
Approval Year	2016	4 (11.4)	9 (13.6)
	2017	12 (34.3)	16 (24.2)
	2018	11 (31.4)	22 (33.3)
	2019	8 (22.9)	19 (28.8)
Cancer Type	Bladder	7 (20.0)	1 (1.5)
	Breast	2 (5.7)	14 (21.2)
	Colorectal	2 (5.7)	0
	Gastric	1 (2.9)	1 (1.5)
	Head and Neck	1 (2.9)	2 (3.0)
	Kidney	0	7 (10.6)
	Liver	2 (5.7)	4 (6.1)
	Lung	8 (22.9)	15 (22.7)
	Neuroendocrine tumors	0	2 (3.0)
	Ovarian	2 (5.7)	5 (7.6)
	Prostate	0	6 (9.1)
	Skin	3 (8.6)	4 (6.1)
	Tumor agnostic	3 (8.6)	0
	Other	4 (11.4)	5 (7.6)
Mechanism of Action	Antibody drug conjugate	2 (5.7)	1 (1.5)
	Androgen receptor inhibitor	0	6 (9.1)
	Immune checkpoint inhibitor	18 (51.4)	19 (28.8)
	Molecularly-targeted drug	11 (31.4)	34 (51.5)
	Combo	3 (8.6)	3 (4.5)
	Other	1 (2.9)	3 (4.5)
Review Process	Breakthrough therapy	22 (62.9)	21 (31.8)
	Accelerated approval	26 (74.3)	3 (4.5)
	Fast track	2 (5.7)	5 (7.6)
	Priority review	34 (97.1)	46 (69.7)
	Orphan	10 (28.6)	14 (21.2)

Abbreviations: RCT randomized controlled trial, SAT single-arm trial

Identification of best comparison therapy

The treatments identified as BCTs for each of the 31 approved indications are shown in Table 2 [10-29]. For avelumab (#6) and pembrolizumab (#13), chemotherapy was used in clinical practice, but there is no standard or consensus regimen. For nivolumab (#20), best supportive care was used in clinical practice as the standard-of-care for this treatment line. For the other 28 indications, we could identify a BCT according to the criteria stated above (Fig. 1).

Table 2 List of investigated products

#	Product	FDA Approved Date	Indication	ORR	BCT	ORR of BCT	Reference of BCT
1	Crizotinib (Xalkori)	March 11, 2016	Metastatic NSCLC whose tumors are ROS1-positive	66.0%	Paclitaxel+Carboplatin+ Bevacizumab	35%	Sandler et al.[10]
2	Atezolizumab (Tecentriq)	May 18, 2016	Locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy	14.8%	Vinflunine	9%	Drugs@FDA [11]
3	Pembrolizumab (Keytruda)	August 5, 2016	Recurrent or metastatic head and neck squamous cell carcinoma with disease progression on or after platinum-containing chemotherapy	16.0%	Cetuximab	13%	Vermorken et al. [12]
4	Rucaparib (Rubraca)	December 19, 2016	Deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies	54.0%	Olaparib	34%	Drugs@FDA [13]

5	Nivolumab (Opdivo)	February 2, 2017	Locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with a platinum-containing chemotherapy	19.6%	Atezolizumab	14.8%	See the result of #2
6	Avelumab (Bavencio)	March 23, 2017	Metastatic MCC	33.0%	NA		
7	Brigatinib (Alunbrig)	April 28, 2017	Metastatic ALK-positive NSCLC who have progressed on or are intolerant to crizotinib	53.6%	Alectinib	44%	Drugs@FDA [14]
8	Durvalumab (Imfinzi)	May 1, 2017	Locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy	17.0%	Nivolumab	19.6%	See the result of #5
9	Avelumab (Bavencio)	May 9, 2017	Locally advanced or metastatic UC whose disease progressed during or	16.1%	Nivolumab	19.6%	See the result of #5

			following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy					
10	Pembrolizumab (Keytruda)	May 18, 2017	Locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy	28.6%	Carboplatin+Gemcitabine	36.1%	Santis et al [15]	
11	Dabrafenib and Trametinib (Tafinlar and Mekinist)	June 22, 2017	Metastatic NSCLC with BRAF V600E mutation	61.0%	Paclitaxel+Carboplatin+ Bevacizumab	35%	Sandler et al [10]	
12	Nivolumab (Opdivo)	July 31, 2017	dMMR and MSI-H metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan	28.0%	TAS-102	1.6%	Mayer et al [16]	
13	Pembrolizumab (Keytruda)	September 22, 2017	Recurrent locally advanced or metastatic, gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1. Patients must have had disease progression on or after two or more prior systemic therapies,	13.3%	NA			

			including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2/neu-targeted therapy				
14	Nivolumab (Opdivo)	September 22, 2017	HCC in patients who have been previously treated with sorafenib	14.3%	Regorafenib	11%	Bruix et al [17]
15	Abemaciclib (Verzenio)	September 28, 2017	Monotherapy for women and men with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting	19.7%	Eribulin	11.0%	Drugs@FDA [18]
16	Afatinib (Gilotrif)	January 12, 2018	Broadened indication in first-line treatment of patients with metastatic NSCLC whose tumors have non-resistant EGFR mutations	66.0%	Afatinib	50.4%	FDA Drug Approvals and Databases [19]
17	Dabrafenib and Trametinib (Tafinlar and Mekinist)	May 4, 2018	Locally advanced or metastatic anaplastic thyroid cancer with BRAF V600E mutation and with no satisfactory locoregional treatment options.	61.0%	Paclitaxel+Carboplatin	16%	Sosa et al [20]
18	Pembrolizumab	June 1, 2018	Recurrent or metastatic cervical	14.3%	Nab-paclitaxel	28.6%	Alberts et al

	(Keytruda)		cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1)				[21]
19	Ipilimumab (Yervoy)	July 10, 2018	Combination with nivolumab, MSI-H or dMMR metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan	46.0%	Nivolumab	28%	See the result of #12
20	Nivolumab (Opdivo)	August 16, 2018	Metastatic SCLC with progression after platinum-based chemotherapy and at least one other line of therapy	12.0%	NA		
21	Cemiplimab-rwlc (Libtayo)	September 28, 2018	Metastatic CSCC or locally advanced CSCC who are not candidates for curative surgery or curative radiation.	47.0%	Panitumumab	31%	Drugs@FDA [22]
22	Lorlatinib (Lorbrena)	November 2, 2018	ALK-positive metastatic NSCLC whose disease has progressed on crizotinib and at least one other ALK inhibitor for metastatic disease or whose disease has progressed on alectinib or ceritinib as the first ALK inhibitor therapy for metastatic disease.	48.0%	Atezolizumab	14%	Drugs@FDA [23]
23	Pembrolizumab	November 9, 2018	HCC who have been previously	17.0%	Nivolumab	14.3%	See the result of

	(Keytruda)		treated with sorafenib				#14
24	Pembrolizumab (Keytruda)	December 19, 2018	Recurrent locally advanced or metastatic MCC	56.0%	Avelumab	33.0%	See the result of #6
25	Erdafitinib (Balversa)	April 12, 2019	Locally advanced or metastatic UC, that has: • susceptible FGFR3 or FGFR2 genetic alterations, and • progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy	32.2%	Pembrolizumab	21.0%	Drugs@FDA [24]
26	Pembrolizumab (Keytruda)	June 17, 2019	Metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.	19.0%	Nivolumab	12.0%	See the result of #20
27	Entrectinib (Rozlytrek)	August 15, 2019	Metastatic NSCLC whose tumors are ROS1-positive.	78.0%	Crizotinib	66.0%	Drugs@FDA [25]
28	Pembrolizumab plus Lenvatinib (Keytruda plus Lenvima)	September 17, 2019	Advanced endometrial carcinoma that is not MSI-H or dMMR and who have disease progression following prior systemic therapy but are not	38.3%	Bevacizumab	13.5%	Aghajanian et al [26]

			candidates for curative surgery or radiation.				
29	Niraparib (Zejula)	October 23, 2019	Advanced ovarian, fallopian tube, or primary peritoneal cancer treated with three or more prior chemotherapy regimens and whose cancer is associated with HDR-positive status	24.0%	Olaparib	34.0%	Kim et al [27]
30	Enfortumab vedotin-ejfv (Padcev)	December 18, 2019	Adult patients with locally advanced or metastatic UC who have previously received a PD-1 or PD-L1 inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.	44.0%	Docetaxel	10.5%	Drakaki et al [28]
31	Fam-trastuzumab deruxtecan-nxki (Enhertu)	December 20, 2019	Unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting	60.3%	T-DM1	31.0%	Krop et al [29]

Abbreviations: ALK, anaplastic lymphoma kinase, BRAF v-RAF murine sarcoma viral oncogene homolog B1, BRCA breast cancer susceptibility gene, CPS combined positive score, CSCC cutaneous squamous cell carcinoma, dMMR mismatch-repair deficient, EGFR epidermal growth factor receptor, FGFR fibroblast growth factor receptor, HCC Hepatocellular carcinoma, HDR homologous recombination deficiency, HER2 human epidermal growth factor receptor, HR hormone receptor, MCC merkel cell carcinoma, MSI-H

microsatellite instability-high, NA not applicable, NSCLC non-small cell lung cancer, PD-1 programmed cell death receptor-1, PD-L1 programmed cell death ligand 1, ROS1 c-ros oncogene 1, SCLC small cell lung cancer, UC urothelial carcinoma

Comparison of ORRs between the investigated product and BCT

In 23/28 indications (82.1%), the ORR of the investigated product exceeded that of the BCT, and in 16 of these (69.6%), the lower limit of the 95% CI of the ORR of the investigated product exceeded the point estimate of the ORR of the BCT. For seven of these products (7/23), the lower limit of the 95% CI was below the point estimate of the ORR of the BCT, with differences ranging from 1.0% to 3.4% (Fig. 2). For five indications (5/28), the point estimate of the ORR of the investigated product was below that of the BCT: three immune checkpoint inhibitors, i.e., durvalumab (#8), avelumab (#9), and pembrolizumab (#10), for urothelial carcinoma, pembrolizumab (#18) for cervical cancer, and niraparib (#29) for ovarian cancer.

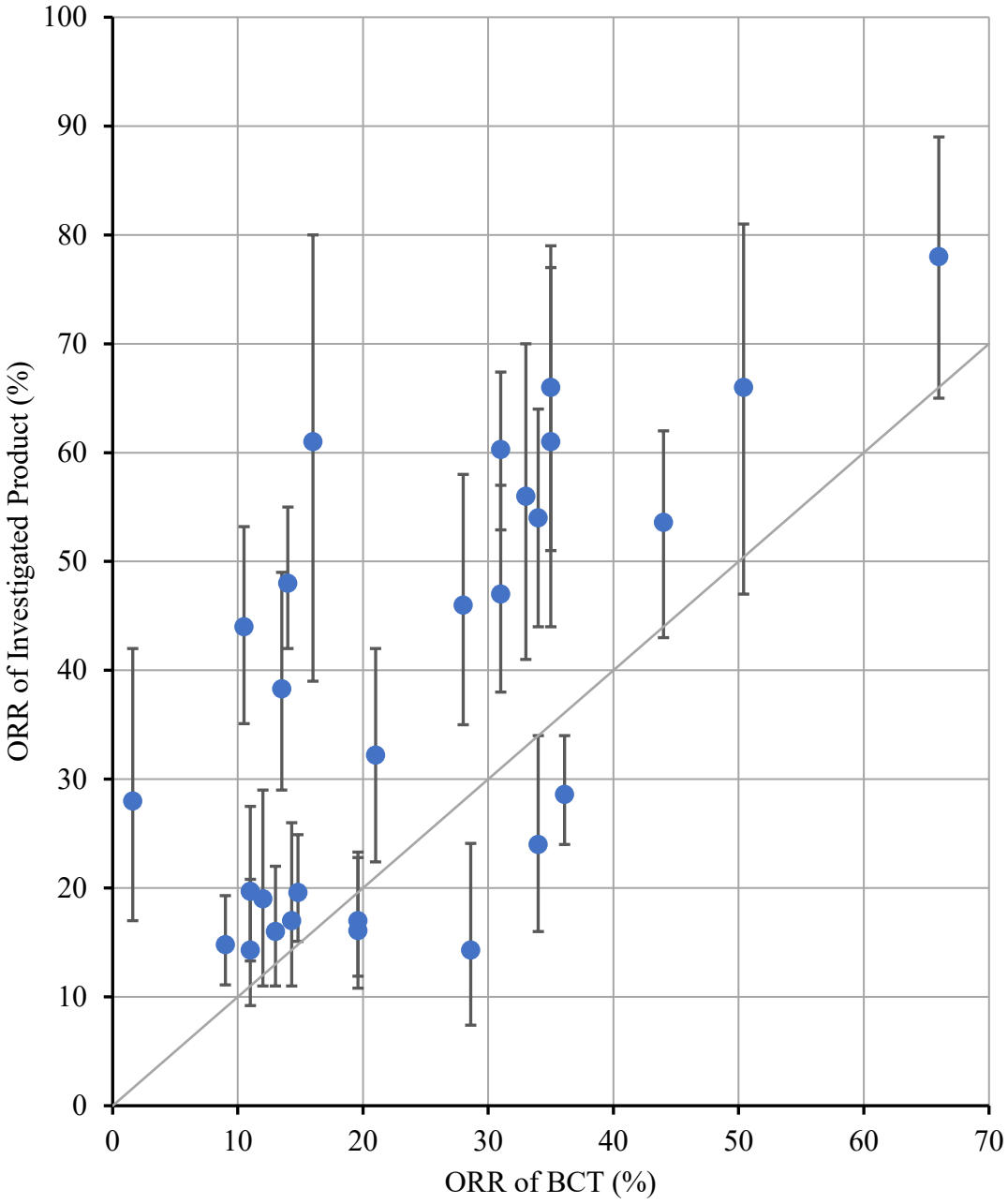


Figure 2 Comparison of ORR between the investigated product and BCT

Abbreviations: BCT best comparison therapy, CI confidence interval, ORR overall response rate

The vertical line in the figure shows the 95% CI of the ORR of investigated product.

2.4. Discussion

In Research 1, the BCTs for each of the indications with SAT approval were identified using objective criteria, and the ORR of the investigated product was compared to that of the BCT. Our results suggested that a 95% CI lower limit of a SAT-based ORR of a new drug that exceeds the point estimate of the ORR of the BCT could be an important factor in deciding on approval of the new drug.

It is well-recognized that a high SAT-based ORR is required for new drug approval. In the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) V1.1, Evaluation Form 3 [30] provides three grades for evaluation of SATs when the primary endpoint is the ORR or progression-free survival. The ORR grade is classified by the degree of the ORR alone or its combination with the duration of response (DOR). For example, an ORR > 60% is rated as Grade 3, while an ORR of 40–60% is considered as Grade 2. Thus, a high ORR is highly valued. In this research, the ORRs of the 28 investigated products ranged from 14.3% to 78.0%. For 13 products (46.4%), the ORRs exceeded 40%. Of these, 11 products were molecular targeted drugs or antibody–drug conjugates. Their high anti-tumor efficacy was demonstrated based on their MOA, which led to their approval. Ten of the 28 products (35.7%) had ORRs of 10–20% (Grade 1 by ESMO-MCBS criteria). Nine of these products were anti-programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) antibodies, which show long-term responses [31]. These products likely obtained approval based on their efficacy, including the DOR, despite their low ORRs. Nevertheless, regardless of the magnitude of the ORR, the lower limit of the 95% CI of the ORR of the investigated product tended to exceed the point estimate of the BCT ORR, suggesting that this could be an important factor in approving the new drug.

There were five indications approved with an ORR below the point estimate of the BCT ORR. The review report for durvalumab, which was approved for second-line urothelial carcinoma, stated that vinflunine was evaluated as a historical control. At the same time, avelumab was also approved for the same indication. The lower limit of the 95% CI of the ORRs of both products exceeded the ORR of 9% for vinflunine. The review report for durvalumab also stated that the ORR was similar to that of other immune checkpoint inhibitors, which had been identified as a BCT in the present research, and it was superior to that of the available chemotherapy. For SAT-based approval, it would be important to establish a comparator that is acceptable to the FDA and that the lower limit of the 95% CI of the new drug's ORR exceeds the ORR of a comparator, rather than comparing it to the latest available therapy at the time of approval.

For pembrolizumab as first-line urothelial cancer, the ORR was 32.3% (95% CI: 26.8–38.1) in a subgroup analysis of patients with PD-L1 combined positive scores (CPSs) ≥ 1%, and 47.3% (95% CI: 37.7. 57.0) in those with a CPS ≥ 10% [32]. For the patient population with a CPS ≥ 10%, the lower limit of the 95% CI for pembrolizumab exceeded the point estimate of the BCT (gemcitabine plus carboplatin) ORR. The NCCN guidelines [33] recommend pembrolizumab for patients with a CPS ≥ 10%, although it is indicated for cisplatin-ineligible urothelial cancer cases, regardless of PD-L1 expression. For pembrolizumab as second-line treatment for cervical cancer, the NCCN guidelines [34] recommend it for patients with a PD-L1 CPS > 1 and DNA mismatch-repair deficient (dMMR) or microsatellite instability-high (MSI-H) cases, but for all other patient subpopulations, recommendations for this drug by the guidelines are rated as category 2B. Pembrolizumab was likely approved as a drug with an expected long DOR, although the ORR was inferior to chemotherapy, in situations with little consensus data.

For niraparib for late-line ovarian cancer, olaparib was expected to be used for patients with BRCA mutations, and niraparib for homologous recombination deficiency (HRD)-positive patients. Niraparib was thought to be approved because some study results showed efficacy in clear patient populations and late-line treatment options are limited.

Ladanie et al. reported that 87% of anticancer drugs approved with SAT results and 50% of anticancer drugs approved with RCT results had received orphan drug designation during 2000–2016 [2]. SATs are considered to be a drug development strategy mainly adopted for new drug applications for rare cancers, in which it is difficult to conduct confirmatory studies. Yet, 28.6% (10/35) of products with SAT-based approval, and 21.2% (14/66) of products with RCT-based approval had received orphan drug designation in the present research, for data collected during 2016–2019. This suggests that the drug development strategy utilizing SATs as pivotal trials is no longer limited to rare cancers. Additionally, even drugs that do not necessarily have a high ORR, such as the newer anti-PD-1/PD-L1 inhibitors, may be considered to have a suitably high ORR, if the sample size were such that the ORR would slightly but statistically significantly exceed the ORR of available therapies. This suggests that the environment for development strategies based on SATs has changed, which may have enhanced SAT-based approvals. On the other hand, Gyawali et al. reported on some anticancer drugs that received AA but failed to improve the primary endpoint in post-approval confirmatory trials [35]. It indicated the importance of understanding the difficulty of evaluating the clinical benefit of new treatments based on limited information such as ORR.

The present research has some limitations. In this research, only approved drugs were included in the analysis, and unapproved or unfiled drugs were not investigated.

There might have been some drugs that showed sufficient ORR in the SAT, but were not approved for some reason; however, it was difficult to identify these facts from the published information. This is an issue for future research.

3. Characteristics of anticancer drugs approved under the accelerated approval program in the US: success or failure in converting to regular approval (Research 2)

3.1. Background

In recent years, drug development based on AA program has been mainly utilized for anticancer drugs. Oncology indications granted AA accounted for approximately 85% of all AAs in the past 10 years [36], and 28 out of 30 AA indications were for anticancer drugs in 2020 [37]. In anticancer drug development, the safety and efficacy of a new drug are explored in phase I and/or phase II, usually with a SAT design. Confirmatory clinical trials, which are often randomized and controlled, are conducted in phase III before new drug application (NDA) [1]. Under the AA program, the NDA is often submitted with preliminary data from exploratory SATs. In the field of oncology, where unmet medical needs still exist, the AA program is recognized as a useful tool for patients to support the early availability of promising new drugs, and for pharmaceutical companies to enable the early launch of new drugs.

The challenge of the AA program is that the FDA cannot always make the best judgment at the time of granting AA because of the trade-off between expedited access to new drugs and the certainty of clinical benefit. In a review of anticancer drugs under the AA program, efficacy was mainly evaluated based on the ORR as the primary endpoint in SATs. ORR is a useful variable in clinical trials because it can be obtained in a relatively short time, and the antitumor effect of the drug can be evaluated objectively, considering the fact that tumors generally do not shrink without treatment. However, ORR and OS may not correlate well, depending on the cancer type and the drugs' MOA [38, 39]. Thus, it provides an uncertain clinical benefit to patients until the drug achieves RA based on

positive results in the confirmatory trial. Therefore, pharmaceutical companies must conduct confirmatory trials within the timeframe agreed upon by the FDA, and act properly when they have a negative result in the confirmatory trial [36, 40]. In addition, it should be ensured that a confirmatory trial is designed to adequately evaluate the clinical benefits [41].

In total, 21 approvals were withdrawn after the implementation of the AA program as of December 2022 [42]. Nearly half (11/21) of the withdrawals were indications approved in 2015 or later, and six were for solid tumors. The failure to demonstrate significant efficacy in confirmatory trials could be attributed to individual factors for each drug [43-48]. Nevertheless, it would be worthwhile to examine the differences between the indications for which AA was successfully converted to RA and those for which AA was withdrawn. This, from the perspective of whether the confirmatory trial was appropriately designed and conducted to verify the efficacy estimated in the pivotal trial for AA (the AA trial). For this purpose, in Research 2, we first investigated and analyzed whether the magnitude of the ORR and the number of subjects in the AA trial, both of which are considered important for designing a confirmatory trial after AA, were related to the subsequent approval status. Second, since the target patient populations in the AA trial and the confirmatory trial were not necessarily the same, we investigated the differences in the trial design, such as the target patient population and treatment regimen, which might have affected the results. In addition, the magnitude of the ORR, as a secondary endpoint in the confirmatory trial, was compared between the experimental and control arms.

3.2. Methods

Identification of products to be investigated

We studied anticancer drugs, including those for additional indications, granted AA by the US FDA, based on SATs, between January 2016 and December 2019. The research period was set by referring to the FDA's Withdrawn/Cancer Accelerated Approval website [42]. This shows that since 2010, there have been withdrawals for solid tumors only in the period between 2016 and 2019. The cut-off date of December 2019 was set because it was thought that sufficient time had passed to conduct subsequent confirmatory trials and verify the results of those trials.

We used same dataset of Research 1. We identified the status of the verification of AA indications from the FDA's Ongoing, Verified Clinical Benefit, and Withdrawn/Cancer Accelerated Approval websites [42, 49, 50] and categorized them into three categories: (1) converted to RA, (2) withdrawn, and (3) study in progress.

We obtained data on the ORR, number of subjects in the AA trial, and information on the MOA of the new drug from the product label. We also obtained information on the primary endpoint, treatment line, regimen, and ORR of the confirmatory trial from the study details and results page of ClinicalTrials.gov [51]. For studies without posted results, data were obtained from published papers.

Data analysis

The number of subjects and point estimates of ORR for the AA trial are shown as box and whisker plots. A scatter plot was created to compare the point estimates of ORR between the experimental and control arms in the confirmatory trials. For 3-arm trials that had 2 experimental arms (monotherapy and combination therapy) and a control arm, data from the combination arm were used. Additionally, a waterfall plot was constructed for

the point estimates of the ORR of the experimental arm minus that of the control arm.

The number of subjects and ORR between AA indications converted to RA and those withdrawn were compared using the Mann-Whitney U test. P values less than 0.05 were considered statistically significant. EZR ver. 1.52 [52] was used for all analyses.

3.3. Results

Identification of investigated products

Of the 31 indications for which ORR was used as the primary endpoint, 24 were granted AA and seven were granted RA. Among the 24 AA indications, 11 were converted to RA and 6 were withdrawn; studies were in progress for the remaining 7 indications (Fig. 3).

The AA indications that were converted to RA and those that were withdrawn are summarized by cancer type and MOA in Table 3. Regarding the cancer type, there were no characteristic differences between the indications converted to RA and those that were withdrawn. For MOA, while six AA indications which have been withdrawn were all immune checkpoint inhibitors (ICIs), those converted to RA included two ADCs, five ICIs, three molecularly-targeted drugs, and one combination therapy.

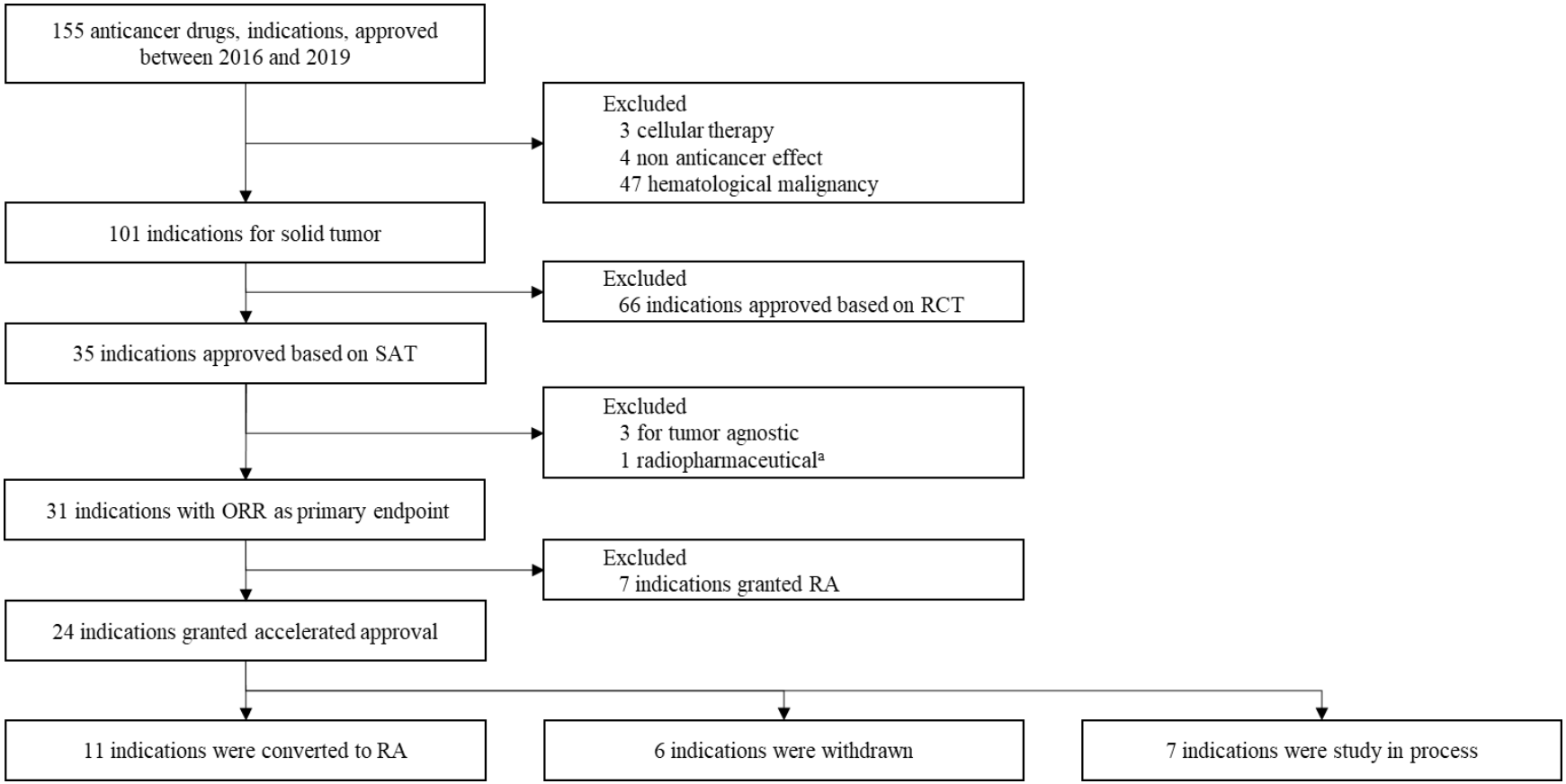


Figure 3 Identification of investigated products for Research 2

Abbreviations: ORR overall response rate; RA regular approval; RCT randomized controlled trial; SAT single arm trial

[a] ORR was not the primary endpoint in the pivotal SAT

Table 3 Characteristics of the AA indications converted to RA and those withdrawn

		Converted to RA n=11	Withdrawn n=6
Cancer Type	Bladder	4	2
	Breast	1	
	Cervical	1	
	Gastric		1
	Head and Neck	1	
	Liver		1
	Lung	2	2
	Ovarian	1	
	Uterine	1	
Mechanism of Action	Antibody drug conjugate	2	
	Immune checkpoint inhibitor	5	6
	Molecularly-targeted drug	3	
	Combo	1	

Comparison of the Characteristics of AA trials between AA indications converted to RA and those withdrawn

Fig 4(a) compares the number of subjects in the AA trials between the indications that converted to RA and those that were withdrawn. There was no significant difference in the number of subjects between the two groups (median, 174 vs. 168; P=0.961). Fig. 4(b) shows a comparison of the ORR in the AA trials. The AA indications that were withdrawn had a significantly lower ORR than those that were converted to RA (median: 38.3 vs. 14.6; P=0.0119).

All withdrawn AA indications were ICIs; therefore, the number of subjects and the ORR for the AA trials for ICI alone were compared between AA indications converted to RA and those that were withdrawn (Fig. 4(c) and 4(d)). There was no difference in the

number of subjects and ORR between the AA indications that converted to RA and those that withdrew.

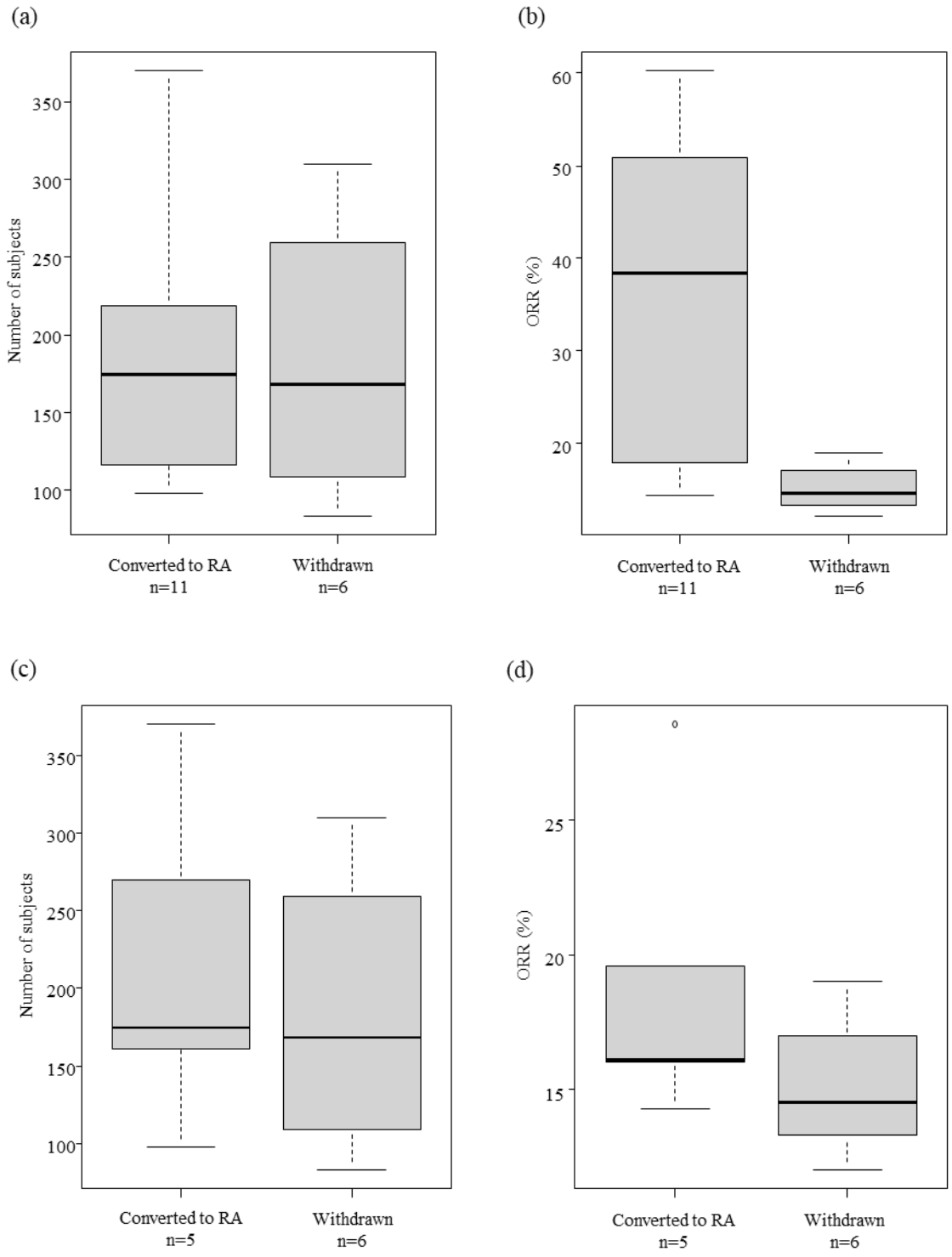


Figure 4　Comparison of the characteristics of the pivotal trial for AA between AA indications converted to RA and those withdrawn

Abbreviations: AA accelerated approval; ORR objective response rate; RA regular approval

Comparison of (a) number of subjects and (b) ORR between AA indications converted to RA and those withdrawn. Comparison of (c) the number of subjects and (d) ORR between AA indications converted to RA and those withdrawn for immune checkpoint inhibitors. The upper and lower boundaries of the central box represent the 75th and 25th percentiles, respectively. The bold horizontal line in each box indicates the median value.

Design of AA trials and confirmatory trials

Table 4 shows the characteristics of the AA and confirmatory trial designs. With regard to treatment lines in the AA trials, one indication was first-line, 10 were second-line, and six were third-line. In the confirmatory trials, 8 indications were first-line, 6 were second-line, and 3 were adjuvant or maintenance therapy. Of the 17 AAs that were converted to RA or withdrawn, 14 (82.4%) had different treatment lines in the AA and confirmatory trials. Among the indications with different treatment lines between the AA and the confirmatory trials, all were changed to earlier treatment lines in the confirmatory trial.

With regard to treatment regimens, 16 indications were single-agent and one was a combination therapy of AA trials. In the confirmatory trials, 11 indications were as single-agents and 6 were as part of combinations. Treatment regimens other than ICIs (five molecular-targeted drugs and antibody drug conjugate indications) were investigated as a single-agent with no changes between the AA and the confirmatory trial, while four indications for ICIs were investigated in combination with chemotherapy, and one was investigated in combination with other ICIs.

Table 4　Characteristics of the trial design of the pivotal trials for AA and the

confirmatory trials after AA

		Converted to RA n=11		Withdrawn n=6	
		AA trial	Confirmatory trial	AA trial	Confirmatory trial
Primary endpoint	ORR	11		6	
	OS		2		4
	PFS		4		
	PFS and OS		4		2
	DFS		1		
Treatment line	First-line	1	5		3
	Second-line	7	3	3	3
	Third-line	3		3	
	Other (adjuvant/maintenance)		3		
Regimen	Single-agent	10	7	6	4
	Combination	1	4		2

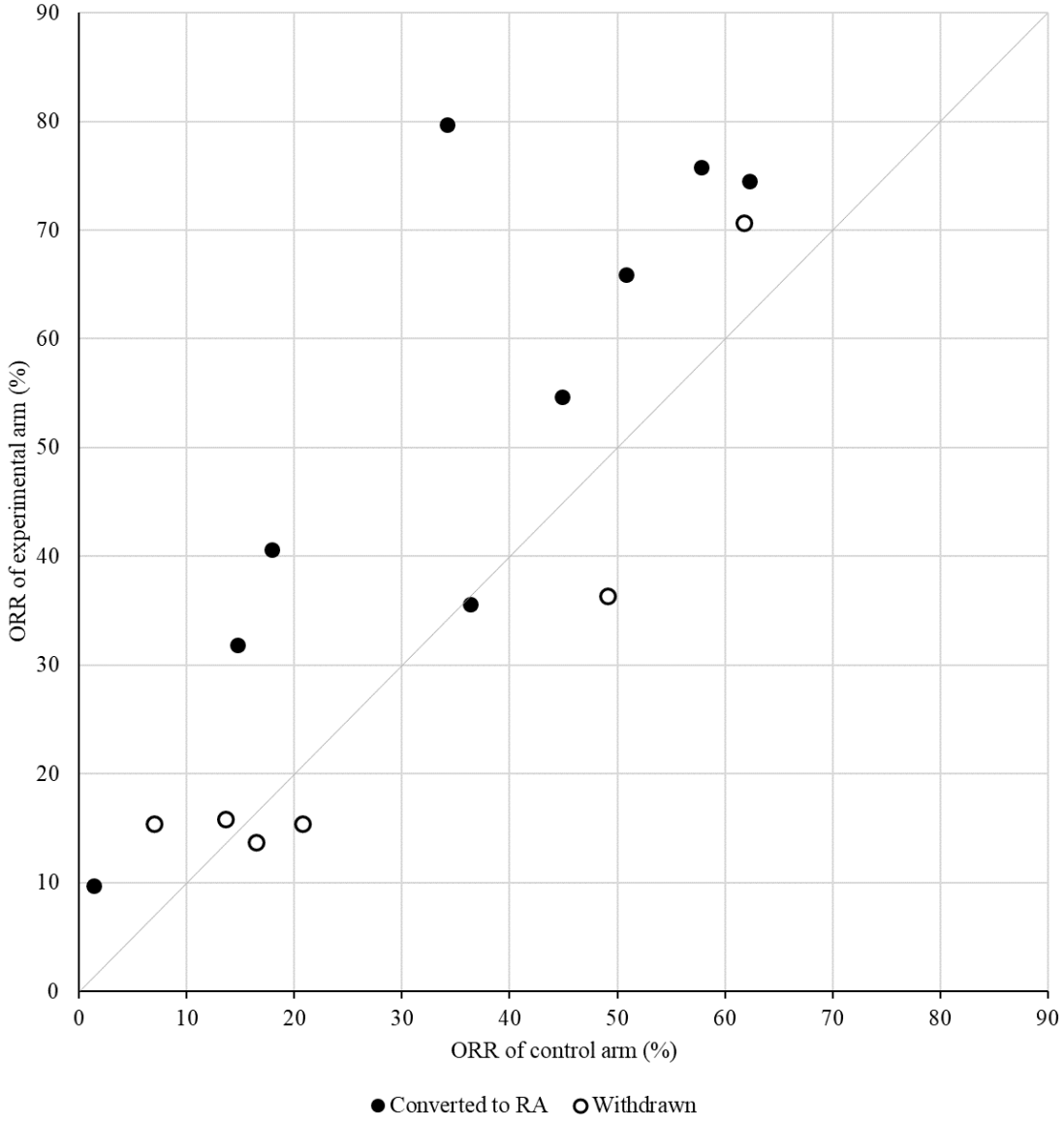
Abbreviations: DFS disease free survival, ORR objective response rate, OS overall survival, PFS progression free survival

ORR for confirmatory trials

We compared the ORR between the experimental and control arms for 15 AA indications, for which the ORR was set as a secondary endpoint in the confirmatory trial, and for which data were available. Among the nine indications that were converted to RA, the ORR of the experimental arm exceeded that of the control arm for eight indications (88.9%). Regarding the withdrawn AA indications, the ORR of the experimental arm exceeded three out of six indications (50%) (Fig. 5 (a)). When we investigated the differences in ORR between the experimental and control arms, all indications with differences greater than the median (8.8%) were converted to RA, whereas 75% (6/8) of the indications for which the difference was less than or equal to the median were

withdrawn (Fig. 5. (b)).

(a)



(b)

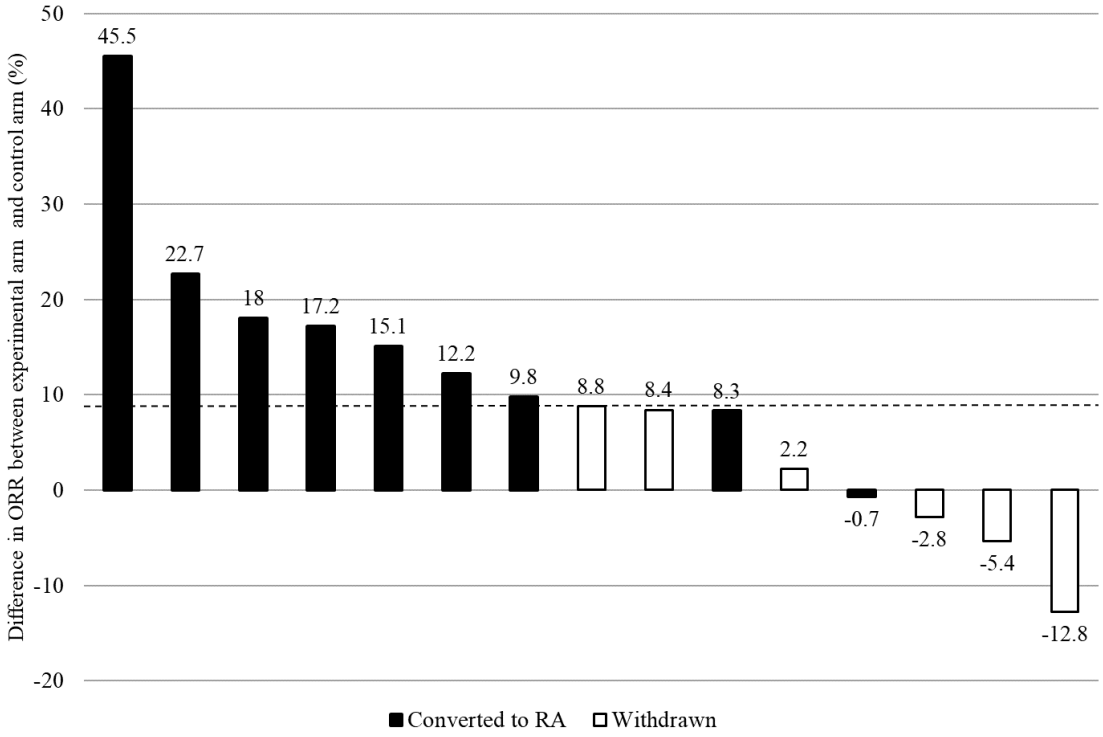


Figure 5 Comparison of ORR between the experimental arm and the control arm in confirmatory trials

Abbreviations: ORR objective response rate; RA regular approval
(a) Scatter plot comparing ORR between the experimental arm and the control arm. (b) Waterfall plot of ORR of the experimental arm minus ORR of the control arm. Black plots/bar are ORR for products converted to RA and white plots/bar are for withdrawn products. The horizontal dotted line in (b) shows the median.

3.4. Discussion

In Research 2, we compared oncology drug AA indications that were successfully converted to RA and those that were withdrawn from the perspective of whether confirmatory trials were appropriately designed, to verify the efficacy estimated in the AA trials. It was difficult to obtain a clear answer regarding the factors that determined the success or failure of the confirmatory trial; however, some points of consideration that

may have affected the success or failure of the trial were obtained.

From the perspective of trial design, confirmatory trials were conducted in patient populations for a different line of treatment than the AA trials in many cases (82.4%). Therefore, it was difficult to compare the data between the AA and confirmatory trials. Some possible reasons why most of the confirmatory trials were conducted in earlier treatment lines are concerns regarding patient enrollment in the RCT because the drug was available in clinical practice after AA had been granted. Additionally, it appears to be a rational decision for pharmaceutical companies to adopt a developmental strategy to expand the indication to an earlier treatment line with more target patients, faster than competing drugs, to maximize the value of the drug. Furthermore, confirmatory trials must be conducted according to a timeline in agreement with the FDA. Initially, we considered that these various constraints would be a risk in the clinical development plan and that changes in trial design from the AA trials would affect the success of the confirmatory trials. However, the present data showed no clear relationship between changes in treatment lines or regimens and success of the confirmatory trials.

There were three indications (converted to RA: two, withdrawn: one) in which AA and confirmatory trials were conducted in the same treatment line. One withdrawn indication was second-line atezolizumab treatment for urothelial cancer. While atezolizumab showed a higher ORR than vinflunine as a historical control in the AA trial (14.8% vs. 9.0%), atezolizumab was compared with chemotherapy (vinflunine, paclitaxel, or docetaxel) in the confirmatory trial, resulting in negative OS as the primary endpoint and a lower ORR compared to the control (15.4% vs. 20.8%). In this case, the magnitude of ORR in the AA trial was confirmed in a confirmatory trial. However, the control treatment differed between the trials, and atezolizumab had a relatively low ORR in the

confirmatory trial.

One of the indications for conversion to RA was pembrolizumab as a first-line treatment for urothelial cancer. In a confirmatory trial, which was conducted as a 3-arm RCT, the combination arm of pembrolizumab and chemotherapy (platinum + gemcitabine) showed a higher ORR than the chemotherapy arm (54.7% vs. 44.9%). Considering the fact that the ORR of the pembrolizumab monotherapy arm in the confirmatory trial was 30.3% and that of AA trial was 28.6%, it can be interpreted that the magnitude of ORR in the AA trial was confirmed in the confirmatory trial. The difference between the above two cases suggests that the probability of success of the confirmatory trial could increase by devising a method to obtain a relatively high ORR, such as the use of a combination regimen.

While the magnitude of the ORR in both the AA and confirmatory trials was not a factor that clearly determined the conversion or withdrawal of AA, it was suggested that a relatively low ORR increased the uncertainty of converting AA to RA. In AA trials, withdrawn AA indications tended to have a significantly lower ORR than those converted to RA. At the same time, because the MOA of the drugs whose AAs were withdrawn were all ICIs, we compared the ORR between the AA trial and the confirmatory trial for ICI indications. This resulted in no difference in the ORR between the AA indications converted to RA and those that were withdrawn. These results suggest that the success of confirmatory trials was not determined by the degree of ORR in AA trials alone but that a low ORR may increase the uncertainty of obtaining positive results in confirmatory trials.

In addition, when the ORR of the experimental and control arms in the confirmatory trial were compared, products converted to RA tended to show a certain degree of increase

in ORR in the experimental arm over the control arm. However, no such tendency was observed for the withdrawn products. The ORR is often a secondary endpoint in confirmatory trials. However, our data suggest that failure to obtain a superior ORR in the experimental arm over the control arm would increase the uncertainty of obtaining positive results in confirmatory trials.

Although the success rate of phase 3 trials of oncology drugs has been reported to be approximately 45% [53], the success rate of confirmatory trials after AA in the present research was 65% (11/17). The fact that there have been a certain number of withdrawn indications suggests that the AA program has been functioning to remove products (indications) that are truly ineffective from the market. However, there is room for improvement in the success rate of confirmatory trials after AA. The data used in the present research were not very large, and the obtained results were not conclusive. However, especially for ICIs with low ORR, the risk of the failure of confirmatory trials may be reduced by selecting appropriate treatment lines, and utilizing combinations with other drugs as necessary so that a higher antitumor effect compared to the control arm can be achieved.

Recently, the FDA issued a draft guidance document [54] aimed at improving oncology clinical trials for AA. It states that, as a limitation of SATs, “low magnitude response rates generally may not be reasonably likely to predict clinical benefit,” which is consistent with the suggestion obtained in the present research. It also recommends conducting RCTs in the AA program, which will have a significant impact on the future development of the AA program.

The present research has some limitations. First, it focused on drugs that were approved based on SAT data; unapproved or unfiled drugs were not investigated. Second,

the number of withdrawn AA indications was small, and important factors, such as the difference in cancer types, should be considered in future studies.

4. Overall discussion and conclusion

In this research, we identified issues to be considered in clinical development of new anticancer drugs, mainly from the perspective of efficacy evaluation, when proceeding with a development plan to obtain approval based on a SAT. In Research 1, we showed that a lower 95% CI limit for the ORR of a new drug in an SAT exceeding the point estimate of the BCT ORR could be an important factor in obtaining regulatory approval. In Research 2, although not being able to identify factors that definitely determine the success or failure of a confirmatory trial conducted after AA, we pointed out that relatively high ORR compared with that of the control arm in the confirmatory trial is important for successfully obtaining RA.

In the present research, it has been demonstrated that not the absolute value, but the relative value of ORR compared to the control treatment is an important endpoint for SATs. In this case, a clinically meaningful ORR would be the ORR that is significantly greater than that of the most current available therapy at the time when the new drug is approved under the AA program. Therefore, in a development strategy aiming for approval based on SATs, it is recommended that the pivotal SAT should be designed to obtain ORR exceeding the figure of the external control, which is a best available therapy at the time of approval of the new drug.

Although most of the confirmatory trials were conducted in patient populations which were different from those in the population for SAT, the ORR of available therapies changes depending on the cancer type and treatment line, and the ORR required for new drugs changes accordingly. Therefore, careful consideration should be given when designing a confirmatory trial, especially for new drugs with low ORR in the SAT. It is desirable to fully discuss the clinically meaningful ORR when planning a development

strategy for a new drug, including consideration of combination regimens according to the MOA or other characteristics of the new drug and selection of patients to be included in the trial.

The goal of treatment with anticancer drugs is to cure the disease, prolong life and palliate symptoms, and the most important endpoint in the development of an anticancer drug is OS. ORR is an objective measure of the anti-tumor effect of a new drug, but it does not necessarily correlate with OS. This is because prolongation of OS is related to various factors such as grade and frequency of adverse events and dose intensity in addition to the antitumor effect. However, our research has demonstrated that clinically meaningful ORR is an important endpoint not only for SAT but also for subsequent confirmatory trials in a development plan aiming for approval based on SAT data as a pivotal trial. We encourage pharmaceutical companies to discuss not only OS and PFS but also ORR as an important endpoint when planning clinical development strategy for new drugs.

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