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Original Article

The Survival and Financial Benefit of Investigator-Initiated Trials Conducted by Korean Cancer Study Group

Bum Jun Kim[1], **Chi Hoon Maeng**[2], **Bhumsuk Keam**[3], **Young-Hyuck Im**[4], **Jungsil Ro**[5], **Kyung Hae Jung**[6], **Seock-Ah Im**[3], **Tae Won Kim**[6], **Jae Lyun Lee**[6], **Dae Seog Heo**[3], **Sang-We Kim**[6], **Keunchil Park**[4], **Myung-Ju Ahn**[4], **Byoung Chul Cho**[7], **Hoon-Kyo Kim**[8], **Yoon-Koo Kang**[6], **Jae Yong Cho**[9], **Hwan Jung Yun**[10], **Byung-Ho Nam**[11], **Dae Young Zang**[1]

**A list of author's affiliations appears at the end of the paper.*

Purpose The Korean Cancer Study Group (KCSG) is a nationwide cancer clinical trial group dedicated to advancing investigator-initiated trials (IITs) by conducting and supporting clinical trials. This study aims to review IITs conducted by KCSG and quantitatively evaluate the survival and financial benefits of IITs for patients.

Materials and Methods We reviewed IITs conducted by KCSG from 1998 to 2023, analyzing progression-free survival (PFS) and overall survival (OS) gains for participants. PFS and OS benefits were calculated as the difference in median survival times between the intervention and control groups, multiplied by the number of patients in the intervention group. Financial benefits were assessed based on the cost of investigational products provided.

Results From 1998 to 2023, KCSG conducted 310 IITs, with 133 completed and published. Of these, 21 were included in the survival analysis. The analysis revealed that 1,951 patients in the intervention groups gained a total of 2,558.4 months (213.2 years) of PFS and 2,501.6 months (208.5 years) of OS, with median gains of 1.31 months in PFS and 1.58 months in OS per patient. When analyzing only statistically significant results, PFS and OS gain per patients was 1.69 months and 3.02 months, respectively. Investigational drug cost analysis from six available IITs indicated that investigational products provided to 252 patients were valued at 10,400,077,294 won (approximately 8,046,481 US dollars), averaging about 41,270,148 won (approximately 31,930 US dollars) per patient.

Conclusion Our findings, based on analysis of published research, suggest that IITs conducted by KCSG led to survival benefits for participants and, in some studies, may have provided financial benefits by providing investment drugs.

Key words Investigator-initiated trials, Survival analysis, Cost analysis, Korean Cancer Study Group

Introduction

Cancer is a leading cause of death worldwide, accounting for 10.0 million deaths in 2019 [1]. In Korea, newly diagnosed cancer cases and deaths in 2020 were reported as 247,952 and 82,204, respectively [2]. It is important to note that cancer prevalence has been generally increasing, largely due to the extended lifespans of people. To improve the prognosis of cancer patients, numerous novel treatment methods, including anticancer agents, are currently under development. Undoubtedly, these novel anticancer therapies have been established based on the achievements of academic clinical research.

Independent academic researchers have traditionally played a pivotal role in the planning and conduct of clinical research, with research conducted by independent researchers classified as investigator-initiated trials (IITs) according to the subject of research. Different from IITs, when a sponsor, mainly pharmaceutical companies, becomes the subject of research, it is classified as sponsor-initiated trials (SITs). As regulatory agencies have strengthened regulations on clinical research and treatment strategies shifted from a disease-specific orientation to a targeted personalized approach, the financial requirements for conducting clinical research have increased dramatically, resulting in SITs replacing the research fields (e.g., late-phase clinical trials) previously covered by IITs [3-5]. Whereas the purpose of SITs is to develop a product intended for large markets to ensure financial success, the primary concern of IITs is scientific investigation, which can generate novel hypotheses. Therefore, IITs tend to have greater interest in niche indications for patients with rare cancers [6,7]. Additionally, comparing the efficacy and safety of drugs from different manufacturers is often a major goal of IITs, and these types of studies are difficult to initi-

Correspondence: Dae Young Zang
Division of Hematology-Oncology, Department of Internal Medicine, Hallym University Medical Center, Hallym University College of Medicine, 22 Gwanpyeong-ro 170beon-gil, Dongan-gu, Anyang 14068, Korea
Tel: 82-31-380-3704 Fax: 82-31-380-1528 E-mail: fhdzang@hallym.or.kr
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ate by pharmaceutical companies [8,9]. IITs are important for advancing medical knowledge, addressing unmet medical needs, and improving patient care by fostering innovation, collaboration, and personalized approaches to treatment. However, greater regulatory burdens and lack of funding are barriers to individual investigators. Under this research environment, it is necessary to prepare a system that can support individual researchers in conducting sound IITs.

The Korean Cancer Study Group (KCSG) is a nationwide multi-institutional cancer clinical trial group established in Korea in 1998. Since its establishment, KCSG has been dedicated to advancing IITs by conducting and supporting multicenter clinical trials. In KCSG, there are a total of 11 disease committees conducting disease-specific clinical studies, including 150 individual researchers from 30 institutions nationwide. KCSG supports IITs by operating an in-house data center. The data center assists individual researchers in conducting IITs successfully by providing clinical research associate (CRA) work, electronic data capture (EDC) setting, data management, and statistical analysis throughout the research process.

In this study, we reviewed IITs conducted by KCSG and quantitatively evaluated the survival and financial benefits of the IITs on cancer patients. In a changing research environment, where it is increasingly difficult for individual researchers to perform IITs, the current obstacles and the ideal role of KCSG as an IIT-supporting organization will be discussed.

Materials and Methods

1. Comprehensive review of IITs conducted by KCSG

Comprehensive review was conducted on IITs conducted through KCSG from 1998 to 2023. Information of newly initiated IITs by year was identified, and information on IITs which was successfully completed and published was collected. The published studies were categorized according to different disease committees to observe their distribution.

To conduct an IIT with the support of the KCSG data center, an individual researcher first undergoes a review by the protocol review committee of KCSG. The time taken from the date of submission to the protocol review committee to the actual publication date of the paper was calculated to determine the duration required for an IIT to start and successfully conclude.

2. Survival analysis

To quantify the survival benefit provided to patients participating in IITs conducted by KCSG, the eligibility for IITs included in the analysis was defined as follows: (1) successfully published IITs conducted through KCSG, (2) interventional randomized controlled IITs, (3) IITs providing progression-free survival (PFS) or overall survival (OS) results.

The PFS or OS gain in each study is defined as the difference between the median PFS or OS in the intervention and control groups. The final survival benefit is defined as "the sum of PFS or OS gain", calculated as the difference between median PFS or OS in the intervention and control groups multiplied by the number of patients in the intervention group. The results were presented in months.

3. Investigational drug cost analysis

To quantify the financial benefit provided to patients participating in clinical studies through IITs conducted by KCSG, the cost of the investigational products provided to patients was calculated. Investigational drug cost analysis was only conducted on certain studies where individual patient raw data was entirely available. To acquire individual patient data such as the number of doses and dosages of investigational products, clinical studies registered in the KCSG data warehouse allowing the extraction of individual patient data were analyzed.

Drug prices were based on information from the Ministry of Food and Drug Safety (MFDS), as of October 2023. For new drugs not priced domestically, drug price information from other countries where prices were established was referenced. We excluded novel drugs that have not yet been approved and therefore have no market cost.

Results

1. Characteristics of IIT conducted through KCSG

From 1998 to 2023, a total of 310 IITs were conducted through KCSG. The number of new IITs initiated each year has been steadily increasing (Fig. 1A). Information on the number of initiated IITs by year is available from 2009, showing a consistent increase over the past 10 years, with more than 20 new IITs starting each year since 2017. Among the studies, the number of successfully published IITs has been maintained steady since 2000, with a total of 133 papers published to date. The number of published IITs by cancer type is evenly distributed (Fig. 1B).

The duration from the start to the successful completion of an IIT was defined as the time difference from the receipt date by the KCSG Protocol Review Committee to the date of publication. Data on study duration was obtained from 56 IIT studies and the median duration of study was 55 months (range, 22 to 185 months).

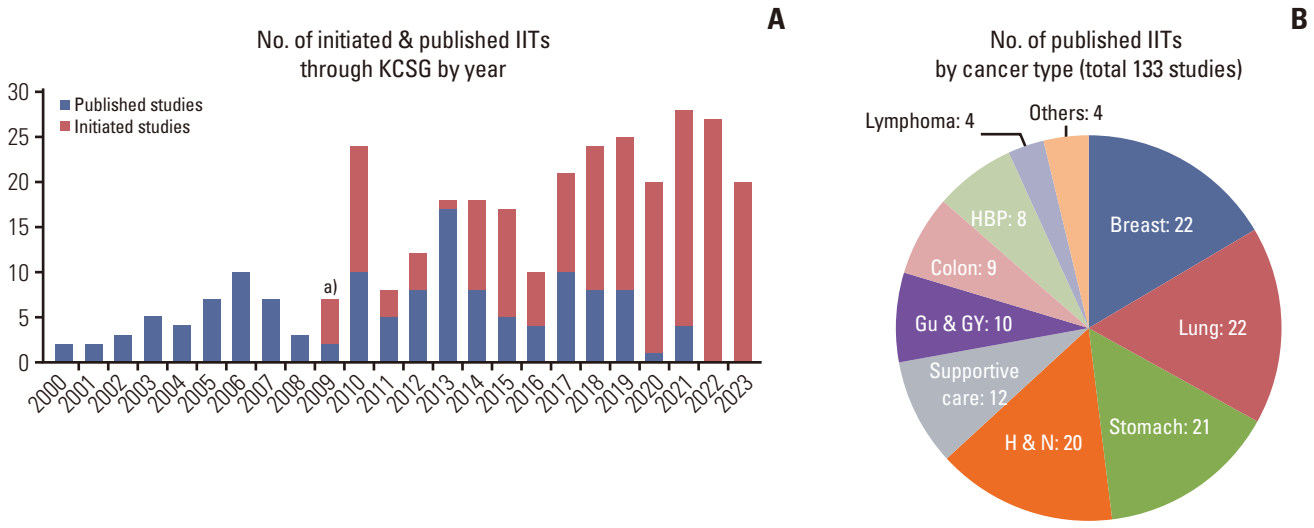

Fig. 1. Number of IITs conducted through KCSG. (A) The number of initiated & published IITs through KCSG by year. (B) The number of published IITs by cancer type. Gu & Gy, genitourinary and gynecologic; HBP, hepatopancreatobiliary; H & N, head and neck; IITs, investigator-initiated trials; KCSG, Korean Cancer Study Group. [a]Data on the number of initiated IITs by year are available since 2009.

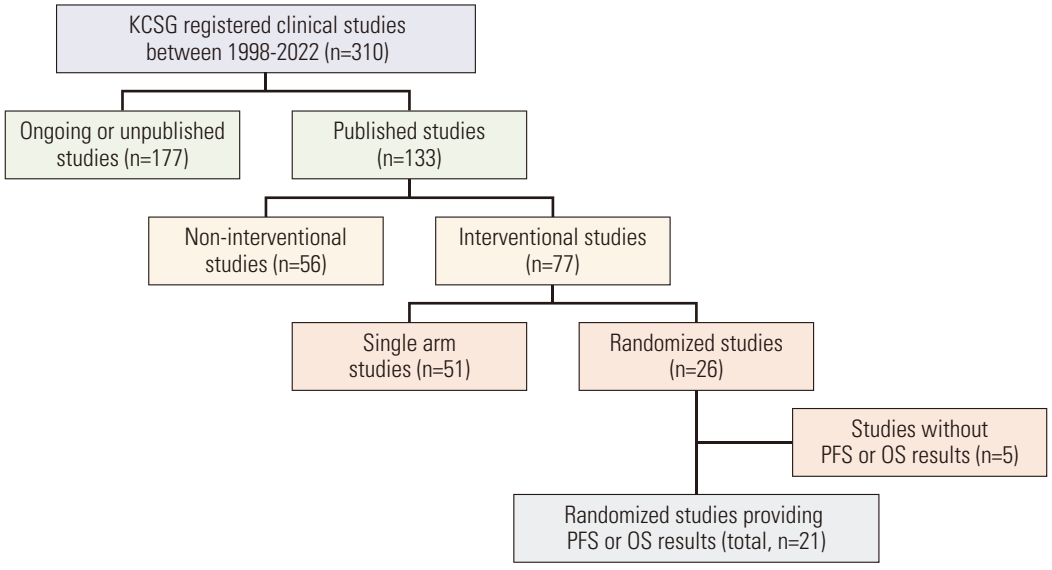

Fig. 2. Flow diagram of included studies. KCSG, Korean Cancer Study Group; OS, overall survival; PFS, progression-free survival.

2. Survival analysis of IITs

Out of the 310 IIT studies conducted through KCSG, 133 were finally published. Excluding non-interventional studies such as observational and retrospective studies, there were 77 interventional studies, among which 26 were randomized phase II or III studies. For quantifying survival benefits, studies not providing PFS or OS results were excluded from the final analysis, and 21 IITs were finally included in the survival analysis regardless of whether they had positive or negative results (Fig. 2).

A total of 1,951 patients in the intervention groups of these 21 clinical studies gained a total of 2,558.4 months (213.2 years) of PFS and 2,501.6 months (208.5 years) of OS, equating to a median PFS gain of 1.31 months and median OS gain of 1.58 months per patient (Table 1) [10-30]. When only statistically significant results were analyzed, PFS gains were identified in 10 studies, with 1,117 patients gaining a total of 1,884.2 months (157.0 years), meaning a PFS gain of 1.69

Table 1. Survival analysis of interventional randomized clinical studies conducted by KCSG

Study code	Phase	Patients	Setting	No. of patients (intervention group)	PFS gain (mo)[a]	Sum of PFS gain (mo)[b]	OS gain (mo)[a]	Sum of OS gain (mo)[b]
1. BR07-02 [10]	Phase III	Breast cancer	1st-line	116	+3.7[c]	+429.2	+8.8[c]	+1,020.8
2. BR11-01 [11]	Phase III	Breast cancer	≥ 1st-line	114	+1.7	+193.8	–3.6	–410.4
3. BR11-16 [12]	Phase II	Breast cancer	≥ 2nd-line	75	+0.9	+67.5	–3.9	–292.5
4. BR13-11 [13]	Phase II	Breast cancer	1st-line	59	+3.0	+177.0	NA	NA
5. BR15-10 [14]	Phase II	Breast cancer	≥ 1st-line	92	+5.7[c]	+524.4	NA	NA
6. BR15-17 [15]	Phase II	Breast cancer	≥ 1st-line	62	+4.2[c]	+260.4	+6.3	+390.6
7. CO06-01 [16]	Phase II	Colon cancer	1st-line	40	–2.2	–88.0	+3.2	+128.0
8. GU10-16 [17]	Phase II	Urothelial carcinoma	1st-line	39	+1.1	+42.9	–1.9	–74.1
9. HN16-08 [18]	Phase II	Adenoid cystic carcinoma	≥ 1st-line	30	+8.0	+240.0	NA	NA
10. LU02-01 [19]	Phase III	NSCLC	1st-line	156	–1.6[c]	–249.6	+1.0	+156.0
11. LU Unknown [20]	Phase II	NSCLC	1st-line	40	+0.0[c]	+0.0	+7.4	+296.0
12. LU05-03 [21]	Phase III	NSCLC	2nd-line	82	–0.1[c]	–8.2	+1.9	+155.8
13. LU05-04 [22]	Phase III	NSCLC	1st-line	209	+1.0	+209.0	+1.2	+250.8
14. LU08-01 [23]	Phase III	NSCLC	2nd-line	68	+6.0[c]	+408.0	+3.3	+224.4
15. LU12-01 [24]	Phase II	NSCLC	2nd-line	80	–0.8	–64.0	+1.3	+104.0
16. LU12-07 [25]	Phase III	SCLC	1st-line	48	+1.9[c]	+91.2	–2.3	–110.4
17. LU12-13 [26]	Phase II	NSCLC	2nd-line	46	–1.0	–46.0	+2.2	+101.2
18. ST02-01 [27]	Phase III	Stomach cancer	1st-line	88	+0.2	+17.6	–0.6	–52.8
19. ST03-02 [28]	Phase III	Stomach cancer	1st-line	139	+0.6[c]	+83.4	+1.2[c]	+166.8
20. ST06-01 [29]	Phase III	Stomach cancer	1st-line	314	+1.1[c]	+345.4	+1.7[c]	+533.8
21. ST10-01 [30]	Phase III	Stomach cancer	2nd-line	54	–1.4	–75.6	–1.6	–86.4
					Total sum of PFS gain	+2,558.4 mo (+213.2 yr)	Total sum of OS gain	+2,501.6 mo (+208.5 yr)

KCSG, Korean Cancer Study Group; NA, not available; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; SCLC, small cell lung cancer. [a]PFS or OS gain is defined as the difference between median PFS or OS in the intervention and control group, [b]Sum of PFS or OS gain is defined as the difference between median PFS or OS in the intervention and control groups × the number of patients in the intervention group, [c]Difference was statistically significant.

months per patient. For OS, three studies showed statistically significant differences, with 569 patients gaining a total of 1,721.4 months (143.5 years) of OS, resulting in an OS gain of 3.02 months per patient.

3. Investigational drug cost analysis of IITs

Investigational drug cost provided to patients from IITs were quantified based on six clinical studies registered in the KCSG data warehouse that had accessible individual patient data. In these six studies, investigational products were provided free of charge to enrolled patients. The results, calculated using patient-specific dosing frequencies, dosages, and per-unit drug price data, are described in Table 2 [31-35]. The total cost of investigational products provided to 252 patients in these six studies was 10,400,077,294 Korean Won (approximately 8,046,481 US dollars), which corresponds to about 41,270,148 won (approximately 31,930 US dollars) per patient. For the investigational product tremelimumab, which is not priced in Korea, the Japanese drug pricing information was referenced.

Discussion

We comprehensively reviewed IITs conducted by KCSG since 1998, analyzing their survival and financial impacts on cancer patients. In our survival analysis, 1,951 patients of 21 studies gained a total of 2,558.4 months (213.2 years) of PFS and 2,501.6 months (208.5 years) of OS, resulting in a median gain of 1.31 months in PFS and 1.58 months in OS per patient. Financially, the total cost of investigational products provided to 252 patients across six studies amounted to 10,400,077,294 Korean Won (approximately 8,046,481 US dollars), averaging about 41,270,148 Korean Won (approximately 31,930 US dollars) per patient.

This study marks the first comprehensive review conduct-

Table 2. Investigational drug cost analysis of 6 IITs conducted through KCSG (using KCSG data warehouse, Trialinformatics)

Study code	Phase	Patients	IP provided (Cost/unit)	No. of patients (receiving IP)	Total cost provided[a)]
1. HN14-01 [31]	Phase II	Salivary gland cancer	Nintedanib (₩29,896/100 mg)	20	₩542,433,024
2. LY14-09 (NCT02433795)	Phase II	Lymphoma	Bendamustin (₩151,971/100 mg) Rituximab (₩897,482/500 mg)	27	₩485,123,177
3. ST14-11 [32]	Phase II	Stomach cancer	Oxaliplatin (₩318,397/100 mg) Irinotecan (₩116,655/100 mg) TS1 (₩3,916/25 mg)	45	₩351,507,606
4. HN15-16 [33]	Phase II	Head & Neck cancer	Durvalumab (₩10,041,606/1,500 mg) Tremelimumab (₩5,574,085/75 mg)	105	₩6,008,340,712
5. LU16-07 [34]	Phase II	Pulmonary sarcomatoid carcinoma	Durvalumab (₩10,041,606/1,500 mg) Tremelimumab (₩5,574,085/75mg)	17	₩1,419,533,095
6. HN17-11 [35]	Phase II	Nasopharyngeal cancer	Nivolumab (₩1,118,490/100 mg) Gemcitabine (₩151,164/1,000 mg)	38	₩1,593,139,680
				Total cost provided in 6 studies	₩10,400,077,294

IP, investigational product; KCSG, Korean Cancer Study Group. [a)]Total cost was calculated using individual patient data, including the number and dose of IP treatments for each patient, obtained through KCSG data warehouse (Trialinformatics).

ed since the establishment of KCSG, signifying the inaugural report of a quantitative assessment of the survival and financial advantages delivered to patients through IITs by a single research organization in the Republic of Korea. When the analysis was limited to studies showing statistically significant results, the PFS and OS gains per patient reached 1.69 months and 3.02 months, respectively, highlighting meaningful improvements in prognosis, particularly considering nearly half of the 21 studies involved patients in a second-line setting or beyond.

Given the challenges posed by regulatory burdens and financial constraints, various countries have established organizations to support IITs. These include the National Clinical Trials Network (NCTN) by the National Cancer Institute (NCI) in the United States [36], the European Organization for Research and Treatment of Cancer [37], and the Japanese Clinical Oncology Group [38], all providing public financial support to enable efficient IIT execution. The South West Oncology Group (SWOG) [39], a key component of the NCI's NCTN, involves over 12,000 members from more than 650 institutions across the United States, enrolling up to 200,000 patients in SWOG trials. With national funding accounting for more than 80% of its operational budget, SWOG's analysis has revealed that IITs orchestrated under its auspices have resulted in a total of approximately 3.34 million life-years saved in the United States, highlighting the critical role of robust public support in the successful implementation of IITs [40].

In the Republic of Korea, individual researchers encounter numerous regulatory challenges in conducting an IIT. Even after successfully developing the study protocol and case report forms, approval must be secured from the Institutional Review Board of the research institution, as well as authorization from the MFDS [41]. Additionally, given the Republic of Korea's national insurance system, approval from the Health Insurance Review & Assessment Service is required for the reimbursement of drugs used in clinical trials [42]. Obtaining these regulatory approvals can take several months, which delays the enrollment of the first patient. Indeed, a nationwide multicenter clinical study involving 24 institutions in the Republic of Korea documented that a median time required for participating institutions from Institutional Review Board submission to first patient enrollment was 4.2 months (range, 1.9 to 10.8 months) [43]. Furthermore, given the long-term follow-up required in IITs, especially those involving cancer patients, the duration from the initiation of an IIT to its successful completion spans several years. Our analysis supports these observations, revealing that among the 56 studies successfully completed through KCSG, the median duration of study was 55 months (range, 22 to 185 months). These findings underscore the necessity for specialized organization equipped to navigate the intricate regulatory landscape. They also underscore the critical role of sustained public financial support in facilitating and invigorating the conduct of non-profit IITs effectively.

KCSG supports IITs through its in-house data center, offering comprehensive assistance in CRA work, EDC settings, data management, and statistical analysis. Recently, KCSG

has been undertaking projects aimed at enhancing its IITs-supporting system with the support of national funding totaling 450 million Korean Won annually (Funding code: HA22C0012, which was decreased by 10% due to recent nationwide reductions in R&D budgets), and KCSG is developing an integrated patient referral system and establishing an independent data monitoring committee to support IITs more efficiently. Considering the results of the investigational drug cost analysis in this study, it can be interpreted that IITs provide cancer patients with the opportunity to receive treatment with high-cost anticancer drugs, which could consequently lead to savings in health insurance finances. Based on these results, from the perspective of cost-effectiveness, it is deemed necessary for the government to provide public funding for the IIT-supporting organization.

Our study has several limitations. First, unlike the SWOG study [40] that included only large-scale phase 3 trials to calculate more precise survival benefits, our analysis incorporated a mix of phase 2 and phase 3 studies, potentially introducing heterogeneity that could affect the results. Due to the lack of research funding support, it was difficult to conduct phase 3 IIT in the Republic of Korea. Second, our survival analysis included clinical studies regardless of whether the results were positive or negative. However, clinical studies that yield negative results generally have a lower probability of publication. Considering this publication bias, our results may have been overestimated. Third, the primary endpoints of the 21 clinical studies included in the survival analysis varied, which may limit the interpretation of the sum of PFS or OS gain, our study's key metric. Lastly, while a comprehensive economic evaluation would require including costs related to treatment outcome, toxicity management from investigational products, our study only calculated the costs of the provided investigational products. Despite these limitations, it is noteworthy that this analysis represents the first report to quantitatively assess the survival and financial benefits delivered to patients through IITs conducted by a single research entity in the Republic of Korea.

In conclusion, our findings, based on analysis of published research, indicate that IITs conducted by KCSG led to survival benefits for participants and, in some studies, may have provided financial benefits by providing investment drugs. To conduct IITs more efficiently and improve the prognosis of cancer patients, it is crucial to enhance the system that supports individual researchers and to secure long-term national funding support.

Ethical Statement

Our study utilized secondary data from previously published literature, hence, the process of obtaining Institutional Review Board approval was omitted. Approval for the secondary use of data was obtained from the principal investigators included in the analysis.

Author Contributions

Conceived and designed the analysis: Zang DY, Keam B.
Collected the data: Keam B, Kim BJ, Maeng CH.
Contributed data or analysis tools: Keam B, Kim BJ, Maeng CH, Im YH, Ro J, Jung KH, Im SA, Kim TW, Lee JL, Heo DS, Kim SW, Park K, Ahn MJ, Cho BC, Kim HK, Kang YK, Cho JY, Yun HJ, Nam BH.
Performed the analysis: Kim BJ, Keam B, Maeng CH.
Wrote the paper: Kim BJ, Keam B.

ORCID iDs

Bum Jun Kim : https://orcid.org/0000-0003-2360-5160
Dae Young Zang : https://orcid.org/0000-0002-2602-7848

Conflicts of Interest

Keam B received research funding from MSD, Bayer, AstraZeneca and Ono Pharmaceutical Co., Ltd., outside of the current work, and has served as an advisor for Handok, NeoImmuneTec, Trialinformatics and ImmuneOncia.
Im SA reports advisory role for AstraZeneca, Novartis, Roche/Genentech, Eisai, Pfizer, Amgen, Hanmi, Lilly, MSD, Daiichi Sankyo, and received research grants through institution from AstraZeneca (Inst), Pfizer (Inst), Roche/Genentech (Inst), Daewoong Pharmaceutical (Inst), Eisai (Inst), Boryung Pharmaceuticals (Inst).
Jung KH reports advisory role for AstraZeneca, BIXINK, Takeda Pharmaceuticals, Novartis, Roche, Gilead, Eisai, Pfizer, MSD, Daiichi-Sankyo, Everest Medicine.
Cho BC reports advisory role for KANAPH Therapeutic Inc, Bridgebio therapeutics, Cyrus therapeutics, Guardant Health, Oscotec Inc, J INTS Bio, Therapex Co., Gilead, Amgen, AstraZeneca, Regeneron, Seagen, Samsung Bioepis, and received research grants from MOGAM Institute, LG Chem, Oscotec, Interpark Bio Convergence Corp, Gradiant Bioconvergence, Therapex, GIInnovation, GI-Cell, Abion, Abbvie, AstraZeneca, Bayer, Blueprint Medicines, Boehringer Ingelheim, Champions Onoclogy, CJ bioscience, CJ Blossom Park, Cyrus, Dizal Pharma, Genexine, Janssen, Lilly, MSD, Novartis, Nuvalent, Oncternal, Ono, Regeneron, Dong-A ST, Bridgebio therapeutics, Yuhan, ImmuneOncia, Illumina, Kanaph therapeutics, JINTSbio, Hanmi, CHA Bundang Medical Center, Daewoong Pharmaceutical Co., Vertical Bio AG, Korea Institute of Oriental Medicine, National Research Foundation of Korea, KHIDI.

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Author Details

[1]Division of Hematology-Oncology, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, [2]Department of Medical Oncology and Hematology, Kyung Hee University Hospital, Seoul, [3]Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, [4]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, [5]Division of Internal Medicine, Center for Breast Cancer, National Cancer Center, Goyang, [6]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, [7]Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, [8]Division of Oncology, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, [9]Department of Medical Oncology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, [10]Department of Internal Medicine, Chungnam National University Hospital, Daejeon, [11]HERINGS, The Institute of Advanced Clinical & Biomedical Research, Seoul, Korea

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